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A

Synthesis of Polyhydroxyindolizidines and Analogues:

A Triple Reductive Amination Approach

By

Hang Zhao

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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THE CITY UNIVERSITY OF NEW YORK

Abstract

Synthesis of Polyhydroxyindolizidines and Analogs: A Triple Reductive Amination Approach

by

Hang Zhao

Adviser: Professor David R. Mootoo

The polyhydroxyindolizidines, castanospermine and swainsonine exhibit potential activity against various glycosidases. They have shown promise in the treatment of cancer and AIDS and other health disorders. As result there has been considerable interest in the synthesis of analogues of those compounds.

Our approach to the polyhydroxyindolizidines relates the target to a tricarbonyl precursor via a triple reductive amination (TRA) reaction. A key step in the preparation of the tricarbonyl precursor was the haloetherification reaction of allylated C5 furanosides or C6 pyranosides. The haloetherification reaction was previously developed in this laboratory. The required allylated saccharide was obtained from the appropriate monosaccharide, through different allylation procedure.

The plan was first tested on castanospermine, and then extended to related polyhydroxyindolizidines, and to pyrrolizidine and quinolizidine analogues. The methodology successfully established the complex bicyclic framework with complete stereocontrol in a single step from the tricarbonyl precursor. The yield of the TRA reaction was somewhat modest for the indolizidines (40 - 50 %), and very low for the quinolizidine (30 %) and pyrrolizidine (20 %).

The mechanism of the TRA was also investigated. The conclusions were based on comparison of the yields and stereochemical results for selected TRA and double reductive amination cyclizations. For the indolizidine systems the reaction could proceed through the intial formation of either a five or six membered ring iminium ion. However, it appears that formation of six membered iminium ion is the favored process. It is also possible that a bicyclic [4·3·0] iminium ion species could be involved. The lower yields obtained for the quinolizidine and pyrrolizidine systems might be an indication of a slower rate of formation of the associated iminium ions, which lead to increased formation of side products resulting from polyamination.

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To my Mom and Dad for loving me unconditionally and for teaching me to look at others in the same light, and to my wife for being the silent push behind me.

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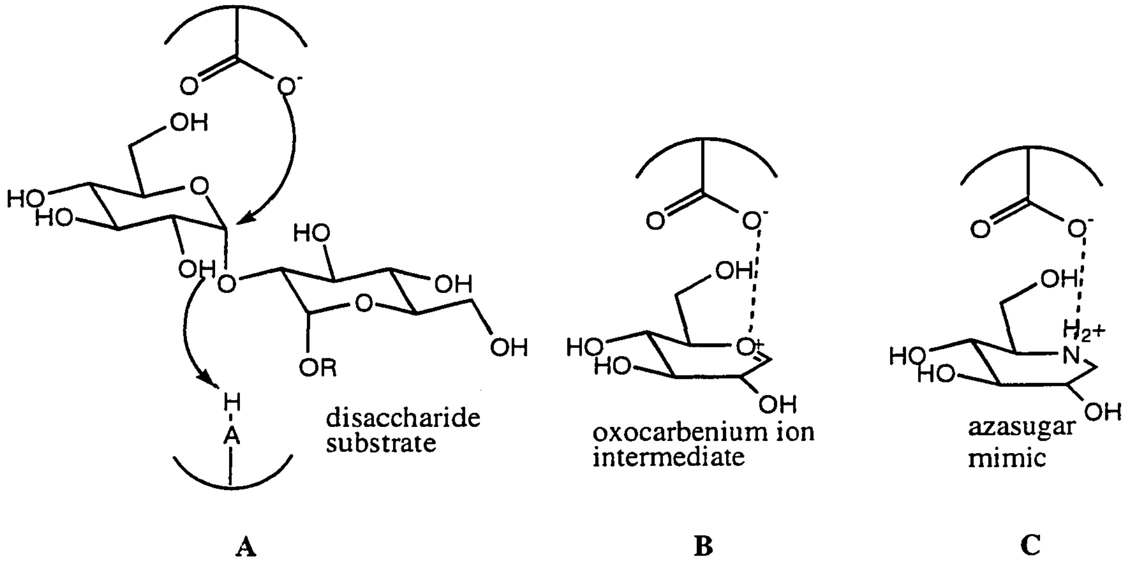
Previous Syntheses of Polyhydroxylated Aza Bicyclo [m.n.0] Systems

I.1 Introduction

The inhibition of glycosidases by azasugars has become an area of vast academic and industrial interest as evidenced by hundreds of publications and patents over the past several years[1]. These enzymes catalyze carbohydrate hydrolysis in important processes such as digestion and glycoprotein biosynthesis. Their role in the trimming of cell-surface oligosaccharides has attracted special attention, because of the implication of these carbohydrates in cellular recognition.

It is believed that, glycosidases act upon the glycosidic linkage of oligosaccharides and glycopeptides by stabilizing an intermediate oxonium ion, thus facilitating the lysis of the glycoside bond (**A** -> **B**). Polyhydroxylated azasugars display similar hydroxylation motifs as the common hexoses, but contain an N in place of the pyranose oxygen. It has been hypothesized that the mechanism of inhibition of glycosidase enzymes by azasugars is a result of the protonation of the nitrogen of the azasugar ring at biological pH. This leads to an electronic mimic (i.e. **C**), of the transition state involved in enzymatic hydrolysis. The protonated amine is believed to interact with the negatively charged carboxylate (in the active site of the enzyme) which is responsible for charge stabilization of the positively charged, high energy oxonium ion during normal hydrolysis[1a,2] **(Fig I-1).**

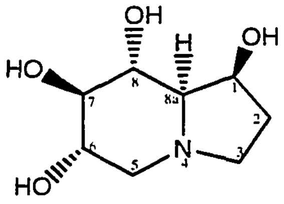
Figure I-1



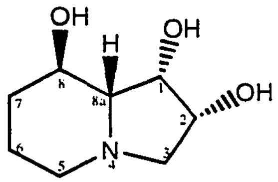
The polyhydroxyindolizidine alkaloids, castanospermine (**I-1**) and swainsonine (**I-2**) are two of the more prominent azasugar derivatives (**Figure I-2**). They are noted for their potent glycosidase inhibitory activity[3]. Analogues have been used as biochemical tools and have been examined as chemotherapeutic agents in the treatment of several disorders, including diabetes,[4] cancer[5] and HIV-I.[6] Their selectivity against specific glycosides has been explained by the resemblance of the spatial arrangement of the hydroxyl groups and the nitrogen to the glycosyl cation intermediate involved in substrate hydrolysis. For example, the activity of castanospermine against glucosidases has been tied to the similarity of six membered ring to the glucosyl cation. In a less obvious way, the anti-mannosidase activity of swainsonine has been related to the resemblance of the five membered ring to the mannosyl cation.

It has been suggested that their rigid, bicyclic structures are responsible for the strong inhibition of certain enzymes and the weak inhibition of others. This theory derives from the observation that related monocyclic 1,5-iminoalditols, which should be more flexible are generally less selective and less potent. In connection with the design of more fine tuned analogues, there has been considerable interest in the synthesis of diastereomeric structures of **(I-1)** and **(I-2)**,[7] and also of the related [4·4·0] and [3·3·0] systems.

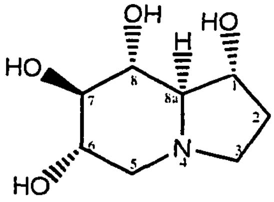
Figure I-2 Polyhydroxyindolizidines: [4·3·0] Systems



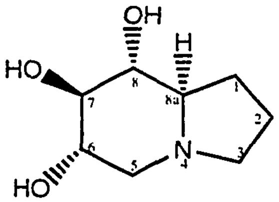
Castanospermine **(I-1)**



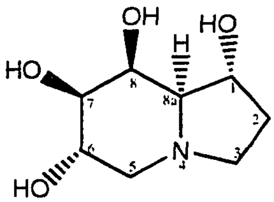
Swainsonine**(I-2)**



1-Epicastanospermine**(I-3)**

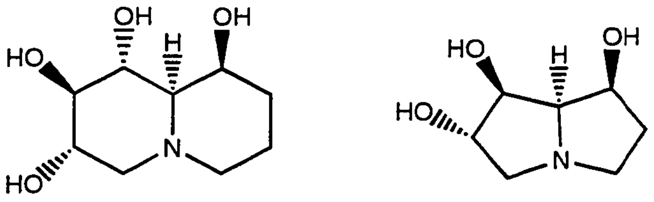


1-Deoxycastanospermine**(I-4)**



1,8-Diepicastanospermine**(I-5)**

Figure I-3 Quinolizidine [4·4·0] and Pyrrolizidine [3·3·0] Systems

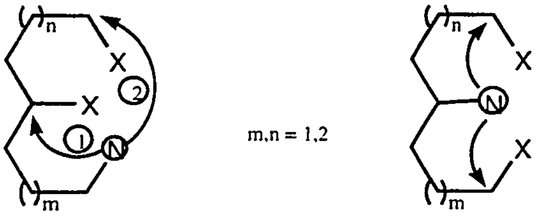


Quinolizidine Analogue **(I-6)** Pyrrolizidine Analogue **(I-7)**

I.2 Review of Syntheses of Polyhydroxyindolizidines and Analogues.

The major synthetic challenges are the stereoselective introduction of the amine, and the construction of the polyhydroxy-bicyclic-aza system with a minimum of functional group transformations.

Two general strategies have been used, type **A** and **B.** These involve the cyclization of a polyol derivatives which contain either a terminal or an internal amino group, respectively.



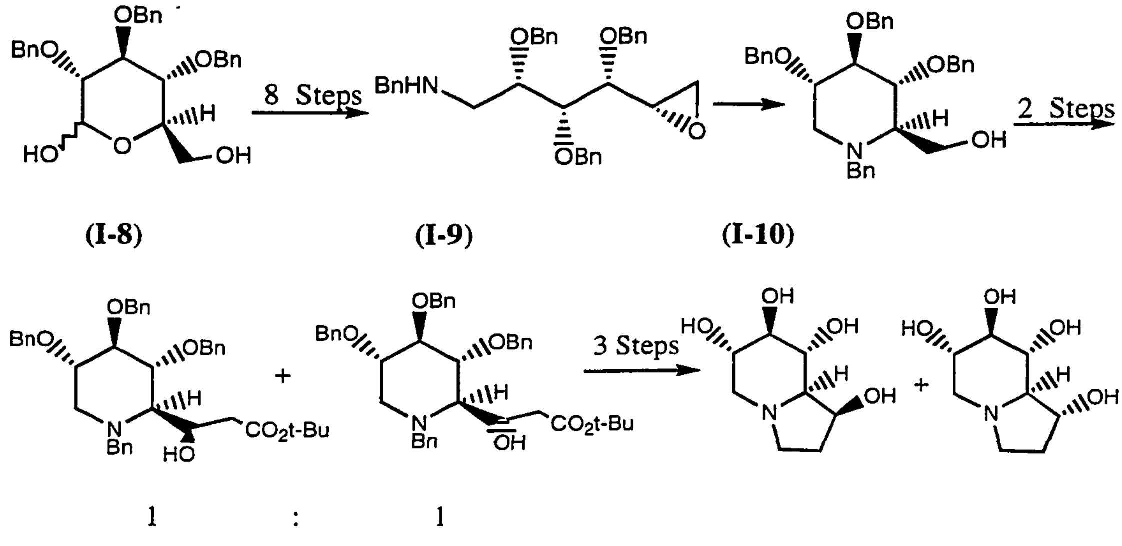
Type A **Type B**

Several different approaches to these amino polyol precursors have been reported. The "sugar-like" structure of the polyhydroxyindolizidines and analogues has led to carbohydrate based strategies in which chiral centers in the product are identified with those in a sugar precursor. Other methodologies involve diastereoselection on simple non-carbohydrate starting materials. Representative syntheses are discussed in the following sections.

Type A: Cyclization of Polyol Derivatives with a Terminal Amine

Ganem and coworkers[8] carried out the first total synthesis of castanospermine **(I-1)**. They used 2,3,4-tri-O-benzyl-α-D-glucopyranose[9] **(I-8)** (obtainable in four steps from methyl-α-D-glucose pyranoside), as starting material. Compound **(I-8)** was transformed in eight straightforward steps to the amino-epoxide **(I-9)**, which cyclized spontaneously and yielded 45 % piperidine **(I-10)**. Oxidation of **(I-10)**, followed by reaction of the resulting aldehyde with t-butyl lithioacetate gave a 1:1 mixture of diastereomers **(I-11)** and **(I-12)**. These product were individually transformed in three steps to castanospermine **(I-1)** and 1-epicastanospermine **(I-4)** respectively. Although relatively long and non-stereoselective, the synthesis established the absolute stereochemistry of castanospermine as (1S, 6S, 7R, 8R, 8aR).

Scheme I-1.

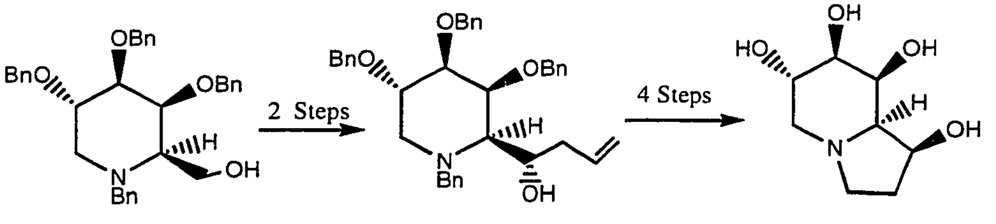


(I-8) (I-9) (I-10)

(I-11) (I-12) (I-1) (I-3)

The stereoselectivity problem was later solved by using a stereoselective Sakurai allylation[10] to establish the C1 chiral center. This reaction gave a single diastereomer (**I-13**) which was converted to castanospermine (**I-1**) in four steps. This methodology was applied to other hexose-derived aldehydes, leading to other analogues of castanospermine.

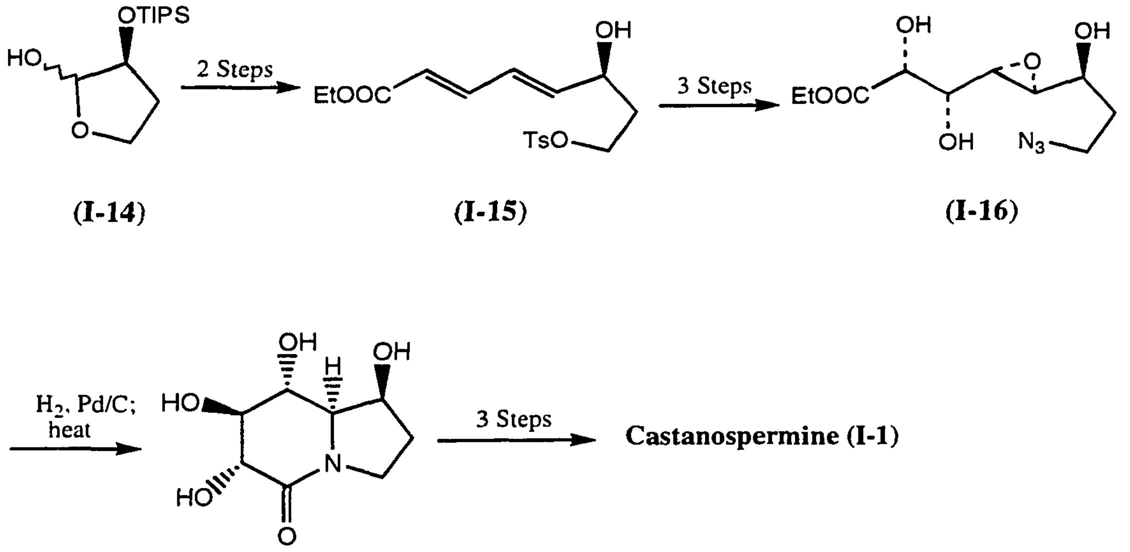
Scheme I-2.



(I-9) (I-13) (I-1)

Cha and Pearson both utilized a reductive double cyclization approach on an azido-epoxide precursor[11,12]. As illustrated in the Cha's synthesis the azide **(I-16)** was reduced to the primary amine, which under the reaction conditions resulted in intramolecular epoxide opening to form indolizidine lactam **(I-17)**. Compound **(I-17)** was converted to castanospermine **(I-1)** in three steps. The azido epoxide precursor was obtained through the diene **(I-15)**, in five steps from readily available lactol **(I-14)**[13,14]. This reaction capitalized on the high diastereoselectivity of the Sharpless epoxidation[15] and dihydroxylation[16] technologies.

Scheme I-3.

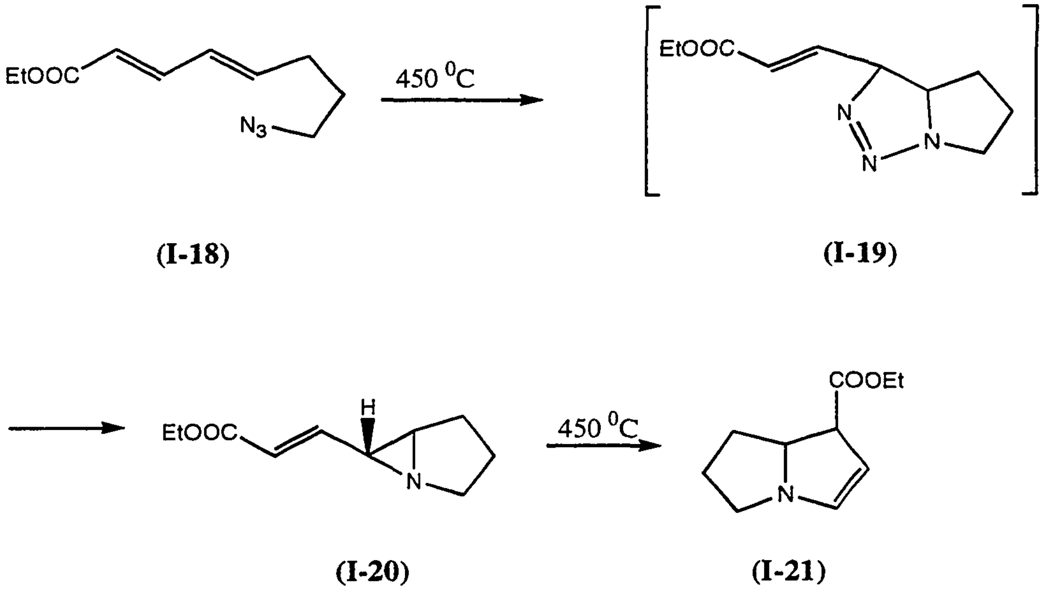


(I-17)

The intramolecular azide-alkene cyclization has been used by several workers to prepare the [m·n·0] aza bicyclic frameworks. In one of the early investigation, the

Hudlicky observed that heating of **(I-18)** to 450 °C gave aziridene **(I-20)**. Compound **(I-20)** was transformed under the reaction conditions, or in a separate step to the pyrrolizidine system **(I-21)**. The formation of **(I-20)** presumably proceeds through triazoline **(I-19)**.

Scheme I-4.

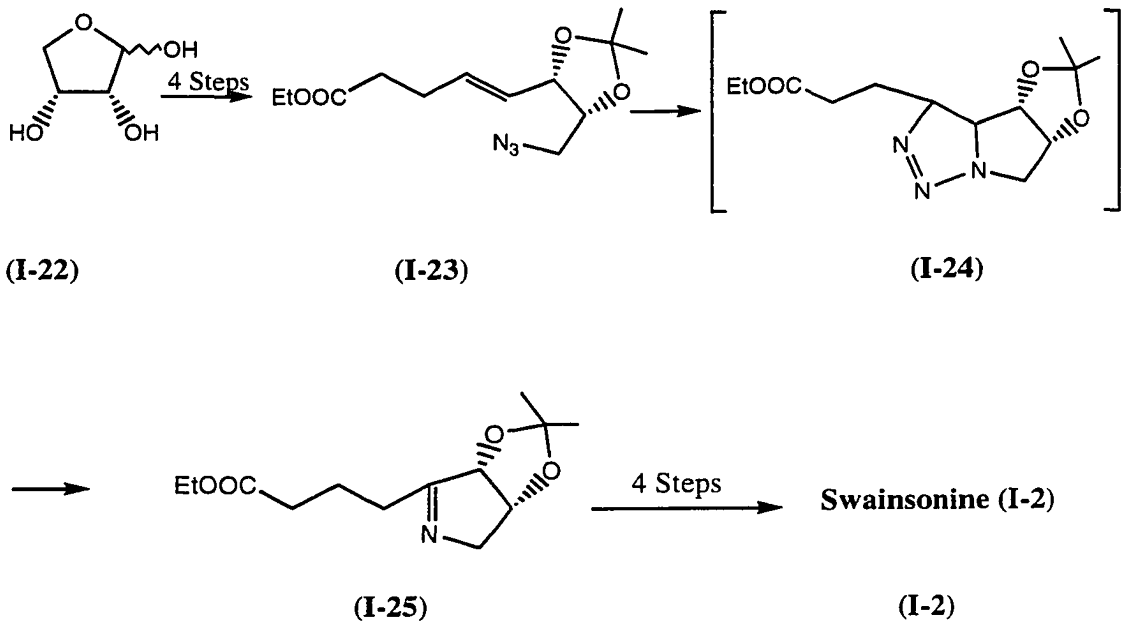


(I-18) **(I-19)**

(I-20) **(I-21)**

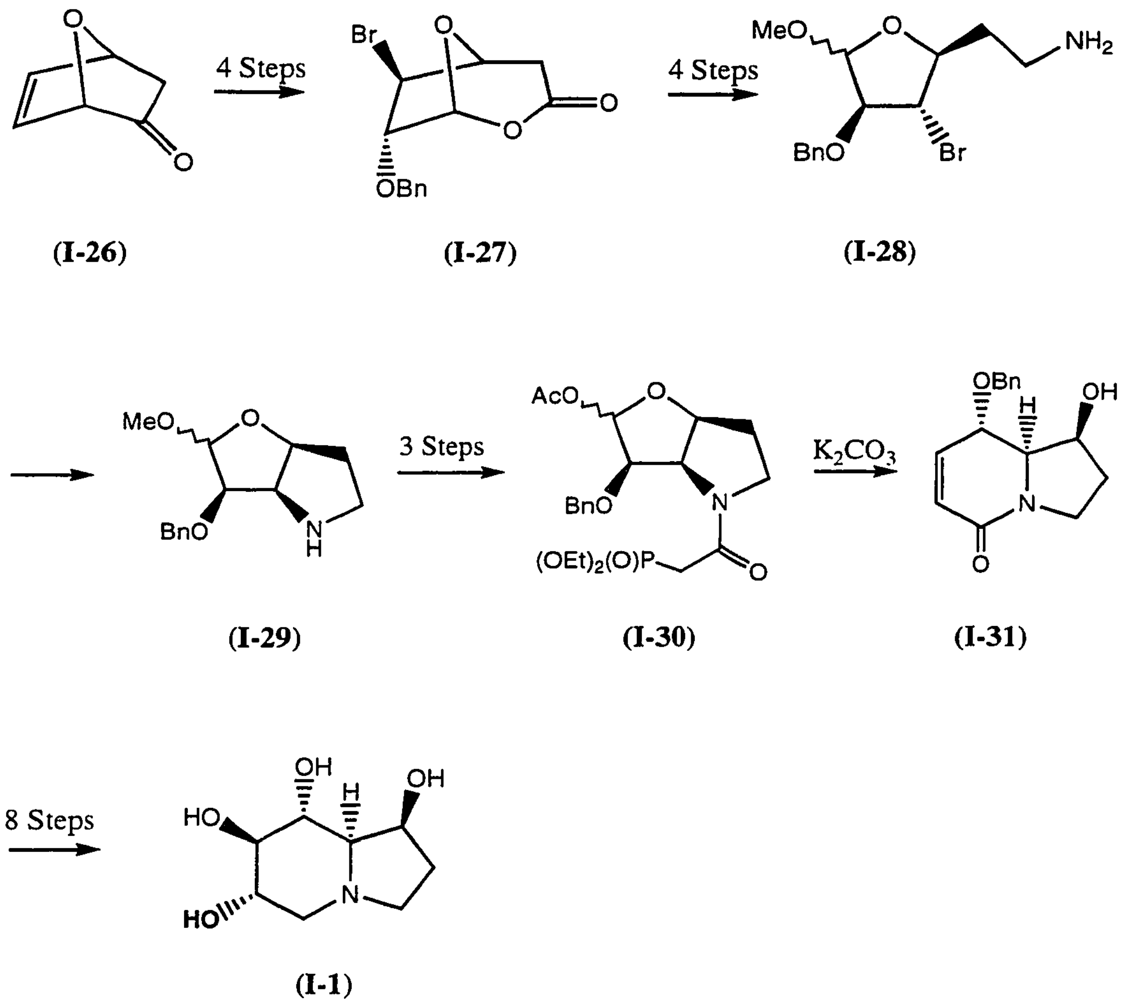
In Cha's work, azide-alkene **(I-23)** cyclized to triazoline **(I-24)**. Extrusion of nitrogen with rearrangement lead to the imine **(I-25)**. It should be noted that in this case, The intermediate triazoline rearrangement to gave the imine, and not aziridene. Swainsonine **(I-2)** was obtained in 4 steps from **(I-25)**. Pearson[19,20,21] and Taber[22] later used a similar approach for assembly of indolizidine and quinolizidine frameworks.

Scheme I-5.



Vogel[23] developed a methodology based on the straightforward, albeit lengthy elaboration of the known Diels-Alder adduct **(I-26)** to the amine **(I-28)**. The intramolecular S_N2 reaction of **(I-28)** gave pyrrolidine **(I-29)**. Compound **(I-29)** was converted to phsphonoacetamide **(I-30)** in three steps. Treatment of **(I-30)** with K_2CO_3 gave **(I-31)** via acetal hydrolysis and an intramolecular Horner-Emmons condensation on the resulting lactol. Castanospermine **(I-1)** was obtained from **(I-31)** in eight steps. This approach was also applied via a type **B** strategy (i.e. cyclization of a secondary amino polyol precursor) to analogues of castanospermine **(I-1)**[24].

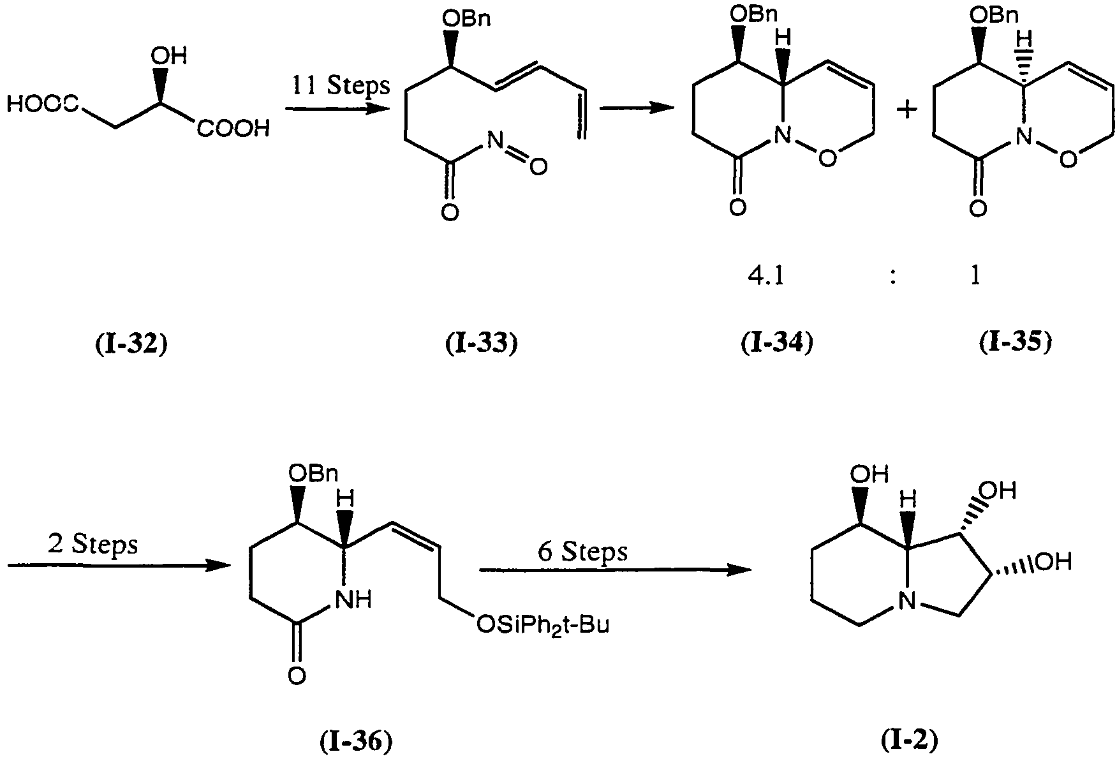
Scheme I-6.



Kiboyashi developed an enantioselective approach to swainsonine **(I-2)** utilizing as a key feature the intromolecular hetero Diels-Alder reaction of the chiral acylnitroso compound **(I-33)**[25]. Compound **(I-33)** was obtained in eleven steps from D-malic acid **(I-32)**. The cycloaddition of **(I-33)** gave a separable mixture of the trans- and cis- 1,2-

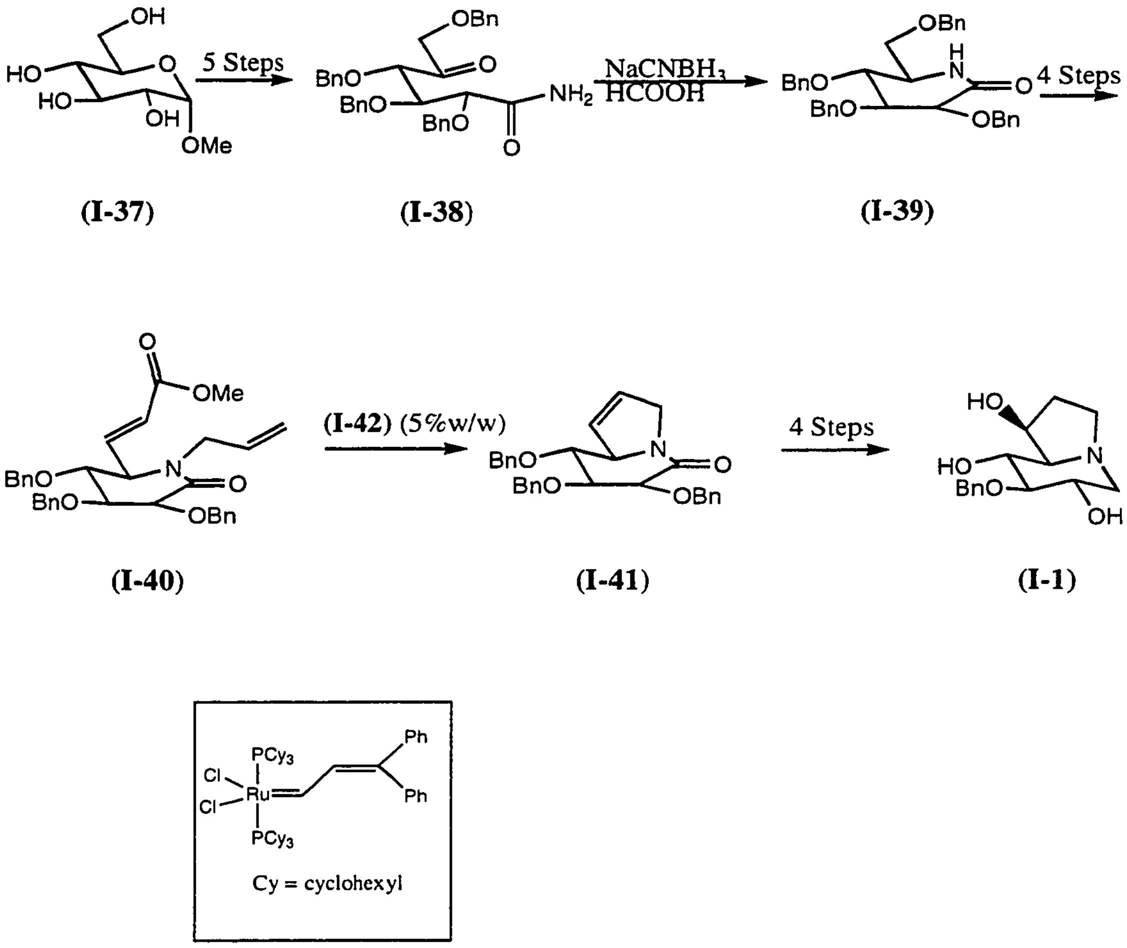
oxazinolactams **(I-34)** and **(I-35)** in a ratio of 4.1 : 1 in 89% combined yield. The major product **(I-34)** was transformed to swainsonine **(I-2)** over eight steps.

Scheme I-7.



Pandit[26,27] developed a novel approach in which a ring closing reaction was used to introduce the second amine ring. The diene precursor **(I-40)** was obtained in ten steps from methyl α-D-glucopyranside **(I-37)**. Treatment of **(I-40)** with the ruthenium carbene complex **(I-42)** as a catalyst, led to form the bicyclic lactam **(I-41)** in 70 % yield. The bicyclic lactam **(I-41)** was converted to castanospermine **(I-1)** (four steps), or to other analogues.

Scheme I-8.



(I-37) (I-38) (I-39)

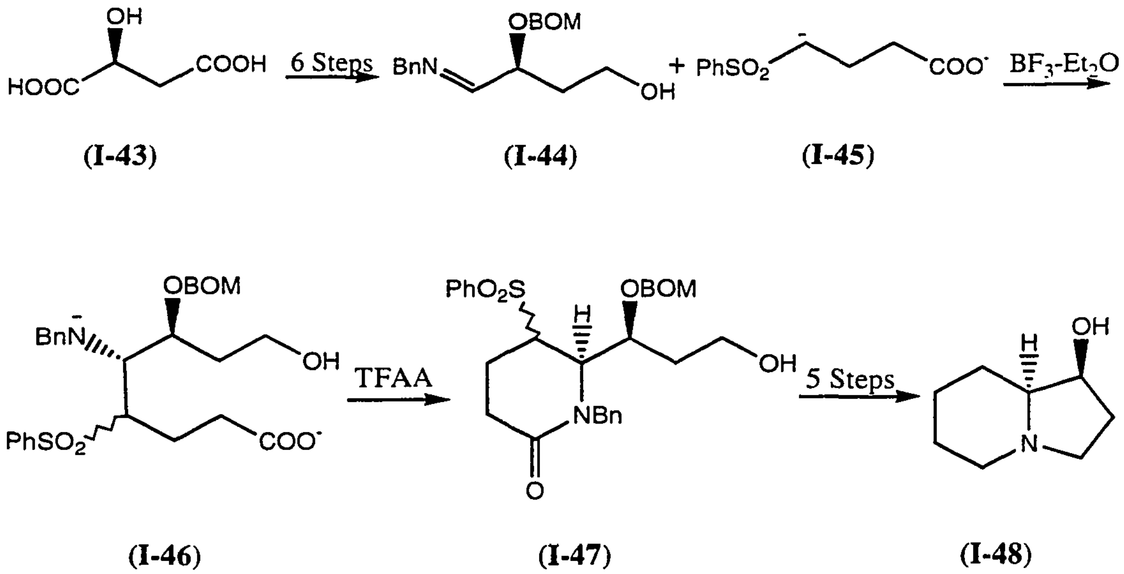
(I-40) (I-41) (I-1)

(I-42)

Type B: Cyclization Polyol Derivatives with an internal Amine

Thompson's[28] approach utilized the diastereoselective addition of the dianion of 4-(phenylsulfonyl)butanoic acid (4-PSBA) **(I-45)** to a chiral α-benzyloxymethyl imine **(I-44)**. This provided a mixture of amines **(I-46)**. In both products, the configuration of the newly formed amine corresponding to that required for the target. The (1S, 8aS)-1-hydroxyindolizidine **(I-48)** was obtained after six straightforward steps.

Scheme I-9.

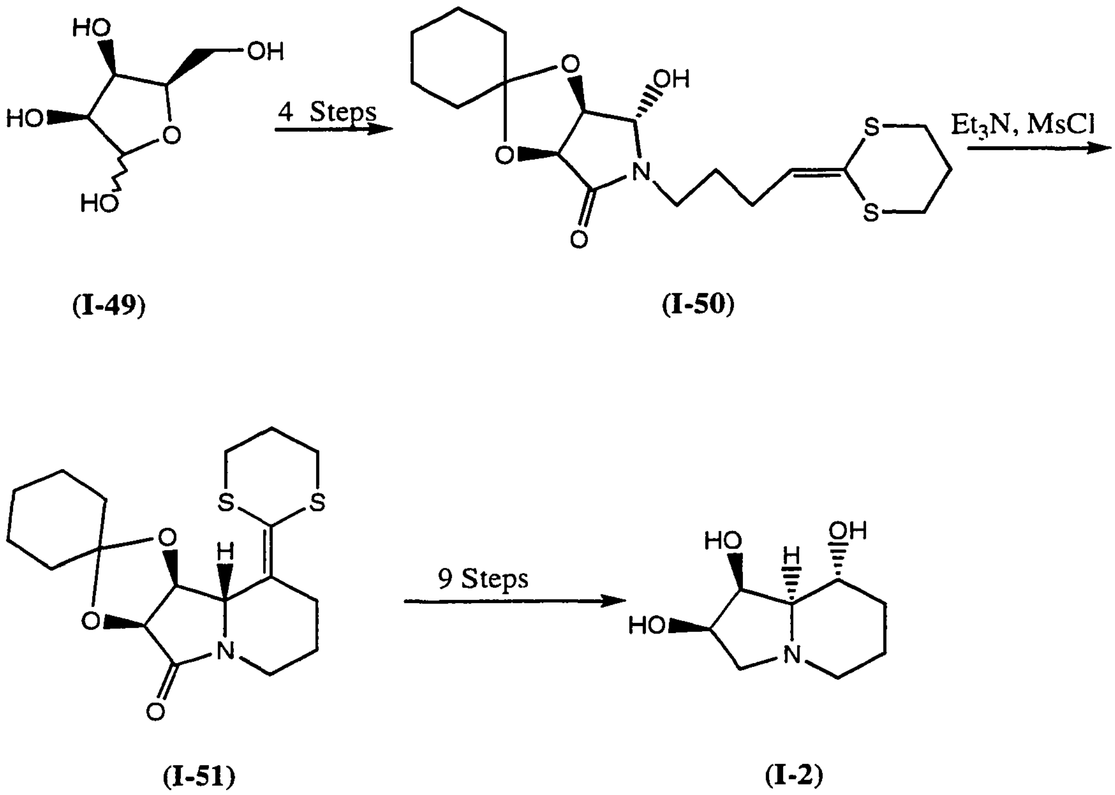


(I-43) **(I-44)** **(I-45)**

(I-46) **(I-47)** **(I-48)**

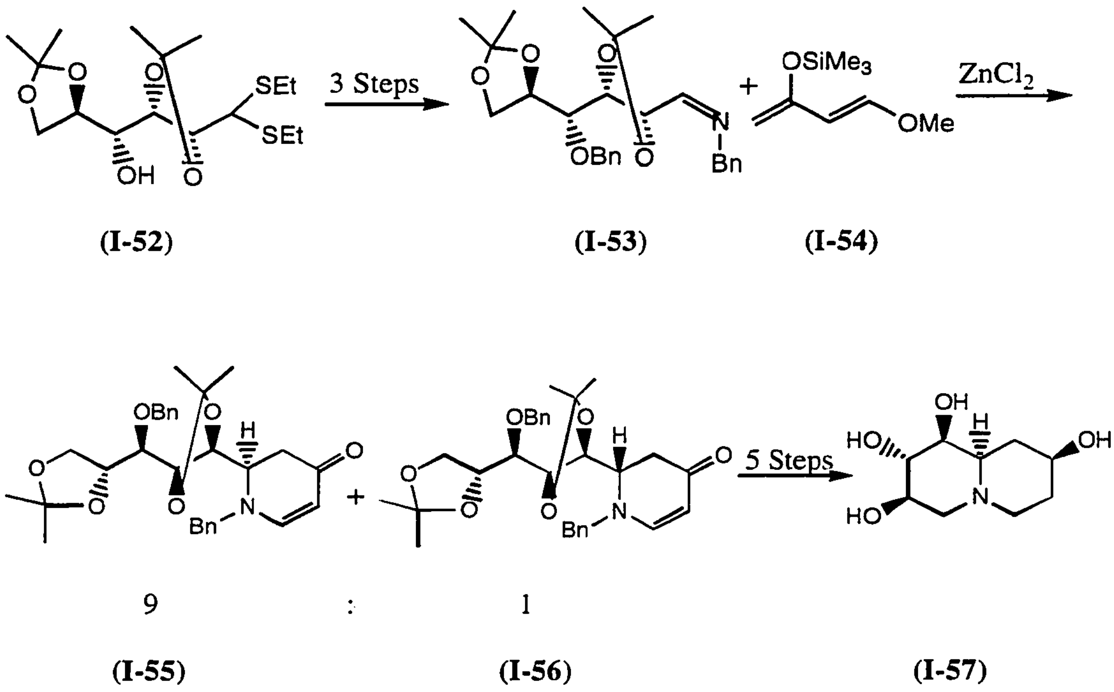
Another strategy in which the C8a amine was introduced by the addition to an iminium species was developed by Chamberlin[29]. This approach was based on the intramolecular addition of a ketene thioacetal to a cyclic iminium ion to give the indolizidine ring system. Thus, treatment of **(I-50)** with methanesulfonyl chloride and triethylamine provided **(I-51)** in 60 % yield. Nine additional steps including the introduction of C8 chiral center led to swainsonine **(I-2)**. This strategy was also used for preparation of castanospermine **(I-1)**.

Scheme I-10.



Herczegh[30] approach to the synthesis of hydroxyquinolizidines involved the hetero-Diels-Alder reactions of sugar-based azomethines **(I-52)**. The reaction of **(I-53)** and **(I-54)** provided a mixture of **(I-55)** and **(I-56)** in a ratio of 9 : 1. The major product **(I-55)** was transformed into **(I-57)** in 5 steps.

Scheme I-11.

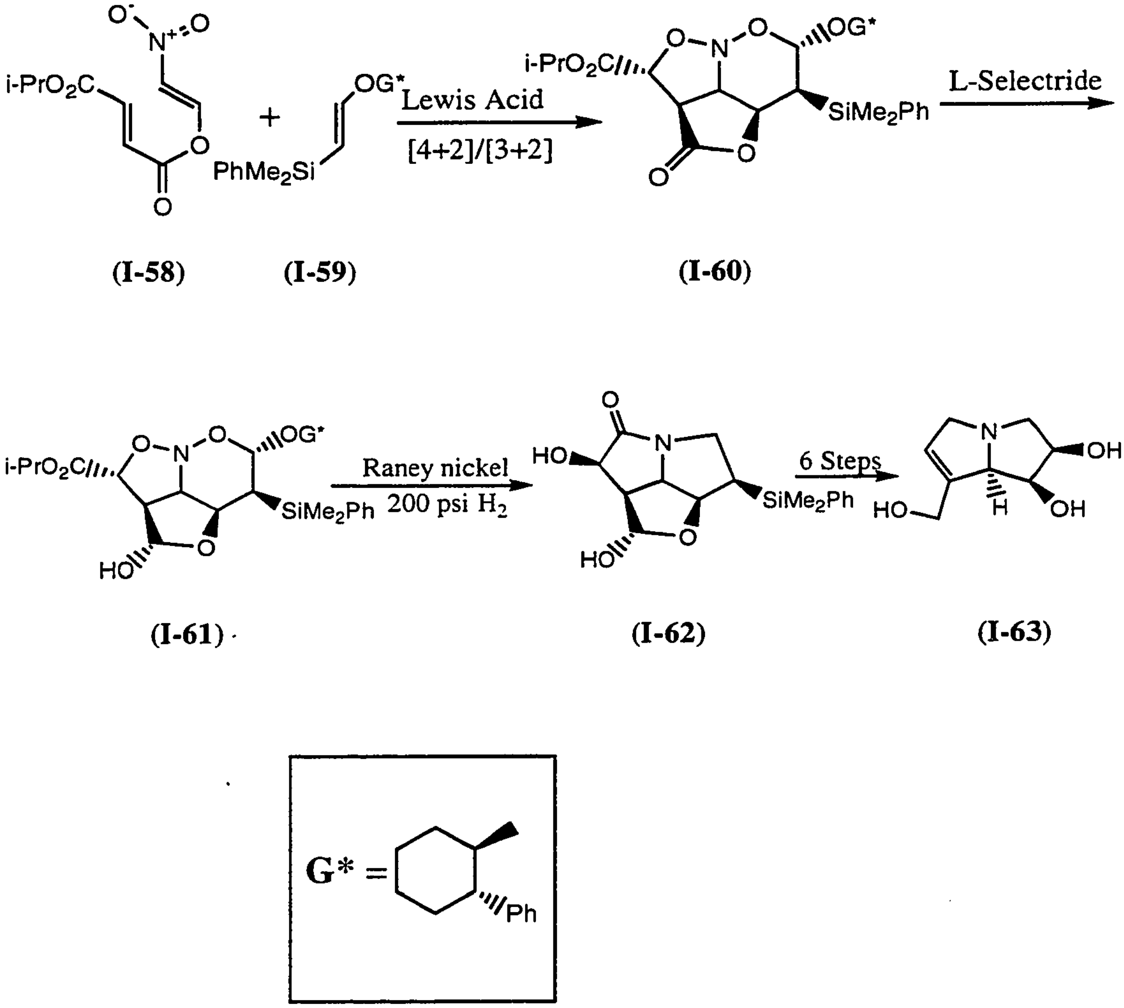


(I-52) (I-53) (I-54)

(I-55) (I-56) (I-57)

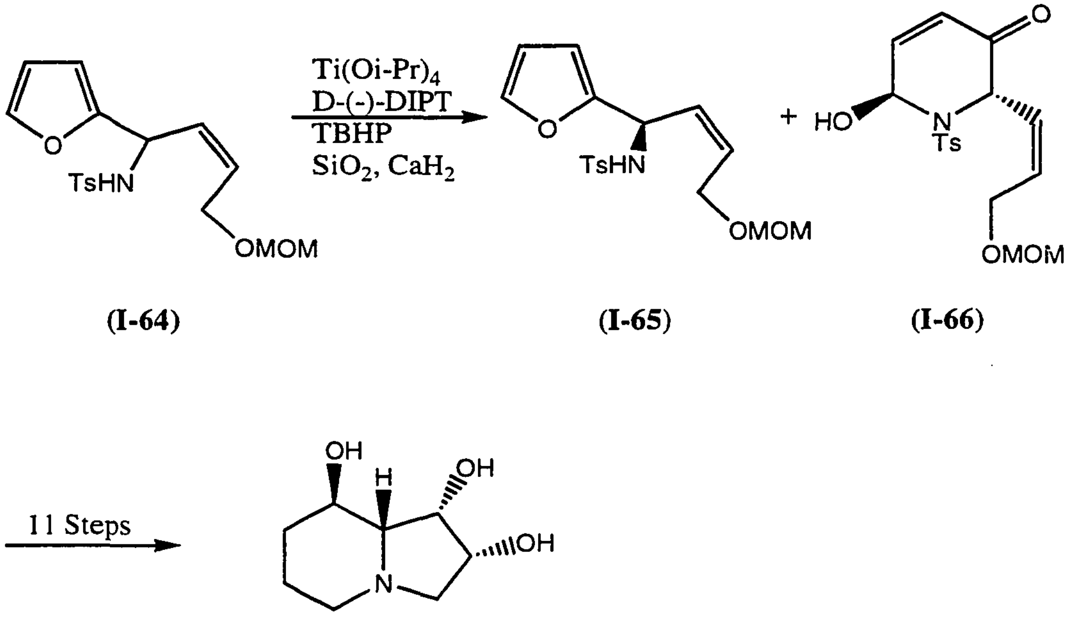
An efficient method for synthesis of pyrrolizidines was worked out by Denmark[31]. The key step is a Lewis acid – promoted, tandem inter [4 + 2] / intra [3 + 2] cycloaddition on nitroalkene **(I-58)** and chiral β-silylvinyl ether **(I-59).** This led to nitro acetal **(I-60).** Compound **(I-58)** was obtained from potassium nitroacetaldehyde with isopropyl fumaroyl chloride. The lactone **(I-60)** was reduced with L-Selectride, followed by hydrogenolysis of the product with Raney Nickel, provided **(I-62).** The final product **(I-63)** was obtained after an additional six steps including reduction, elimination and Tamao oxidation of silyl group. Although this methodology is very powerful for preparation of pyrrolizidines, extension to indolizidines and quinolizidines will be more complicated because of the additional carbons required.

Scheme I-12.



Zhou's[32] synthesis of swainsonine **(I-2)** was based on the oxidation of the α-furfuryl amide **(I-64)** to the prperidinenone **(I-66)**. Kinetic resolution provided the required configuration of the C8a amine. Compound **(I-66)** was elaborated to **(I-2)** in 11 additional steps.

Scheme I-13.



(I-64) (I-65) (I-66)

(I-2)

I.3 Synthesis of [m·n·0] Systems via Reductive Amination Strategies

The aforementioned approaches illustrate some of the general synthetic problems in the synthesis of these aza [m.n.0] systems. In many cases several of the chiral centers in the target are introduced in low stereoselectivity. Secondly several protecting group steps are involving the alcohol groups and the amine. These procedures decrease the overall synthetic efficiency. Thirdly, in a number of syntheses the starting materials are not easily accessible and, or, the reaction procedures are not straightforward. Fourthly the majority of these methods are not general for indolizidine, pyrrolizidine and quinolizidine frameworks.

Approaches in which two cyclic amines are formed in the same reaction are attractive because of the potential for minimizing functional group transformations. Our approach to polyhydroxyindolizidines relates the target to a tricarbonyl precursor via a triple reductive amination (TRA) reaction. The tricarbonyl compound can be derived from the appropriate monosaccharide by straightforward carbohydrate methods. The potential advantages of this approach are:

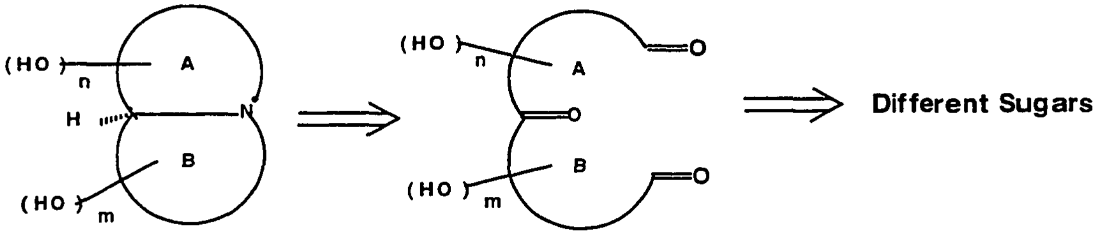
1). The cyclization reaction forms two rings directly, with concomitant introduction of the amine and one chiral center C8a.

2). The starting sugars are commercially available and very inexpensive.

3). Starting with different sugars, different polyhydroxyindolizidines and analogues will be prepared by simply modifying the basic procedure.

4). The TRA strategy may provide a general route to polyhydroxy-indolizidines, polyhydroxy-pyrrolizidines and polyhydroxy-quinolizidines.

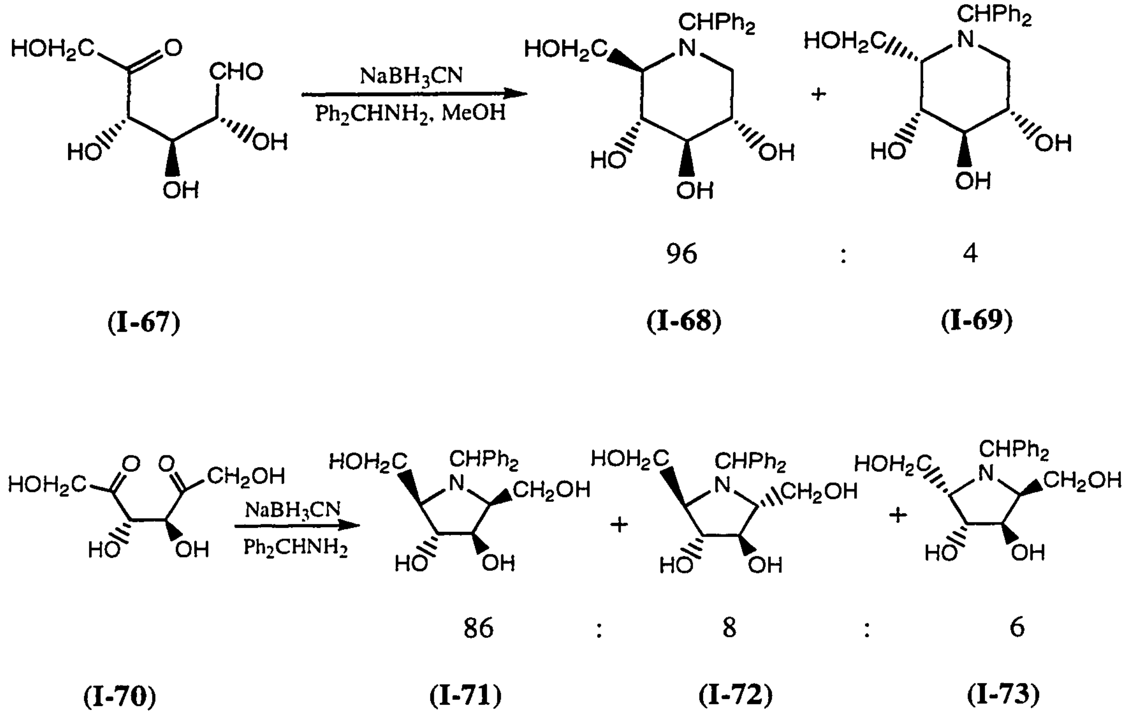
Scheme I-14.



A or B= 5 or 6 membered rings, PG = protecting group

The double reductive amination of dicarbonyl substrates to form piperidines and pyrrolidines is well known. The recent work by Reitz and co-workers[33] is noteworthy in that high stereoselectivity was obtained at one or two newly formed aminated carbons.

Scheme I-15.



(I-67) **(I-68)** **(I-69)**

(I-70) **(I-71)** **(I-72)** **(I-73)**

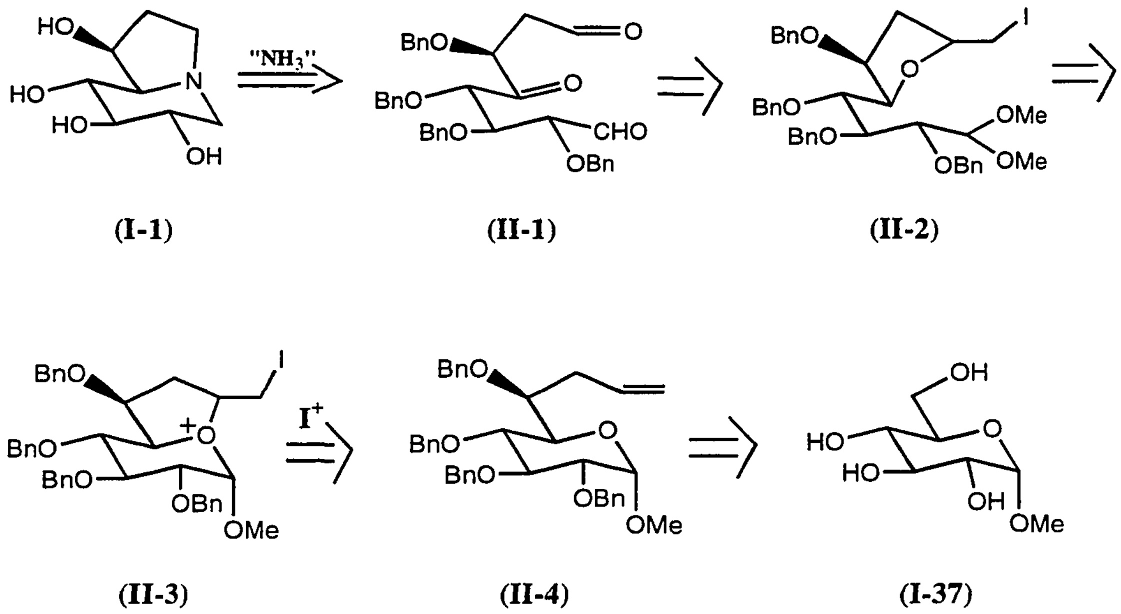
Chapter II

Total Synthesis of Castanospermine

II.1 Retrosynthesis

Castanospermine **(I-1)** may be obtained by the TRA strategy on a tricarbonyl precursor **(II-1)** (Scheme II-1)[34]. The introduction of the amino residue at a late stage in the synthesis, with concomitant formation of the indolizidine framework, could reduce the number of functional group transformations. Potential problems with this approach are the formation of di- and tri- aminated products and low stereoselectivity at C8a. In addition the preparation of the tricarbonyl precursor might not be trivial. Studies from this laboratory have shown that the C6 allylated monosaccharide **(II-4)** on treatment with iodonium ion, in the presence of methanol undergoes a facile, high yielding reaction to a halo-THF acetal **(II-2)**[35]. This reaction involves attack of the ring oxygen as the first formed halonium ion to give the intermediate oxonium ion **(II-3)**, which is converted to **(II-2)**. This suggested a route to the requisite tricarbonyl precursor because the hydroxyl-alkene-acetal obtainable by reductive opening of **(II-2)** can be regarded as a precursor to the keto-dialdehyde **(II-1)**. Since the halocyclization reaction is general for monosaccharides, this approach can be used to access diastereomeric tricarbonyl derivatives. C6 allylated pyranosides of the of the type **(II-4)** are readily available from the parent pyranosides (e.g. **(I-37)**).

Scheme II-1

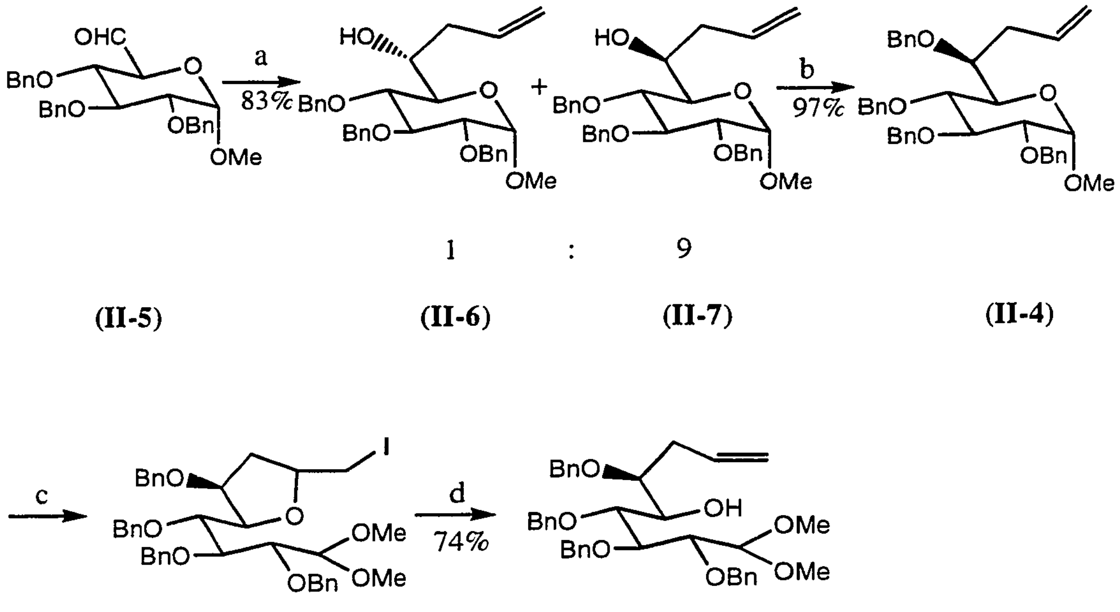


II.2 Synthesis

Allylmagnesium bromide was added to the known aldehyde **(II-5)**[36,37,38] (4 steps from methyl α-D-glucopyranoside). Two isomers **(II-7)** and **(II-6)** in a 1:1 ratio were produced in 78 % yield. When the conditions developed by Whitesides[39] (tin powder and allyl bromide in CH_3CN-H_2O (10:1)) was used, an 83 % yield of **(II-7)** and **(II-6)** in a 9:1 ratio was obtained. The stereochemistry of the products was tentatively assigned by comparison of the NMR with that of related C6-gluco pyranoside alcohols[40]. Chromatographic separation and benzylation of the major product **(II-7),** gave **(II-4)**. Treatment of **(II-4)** with iodonium dicollidine perchlorate (IDCP) / CH_2Cl_2/ MeOH provided a mixture of iodo-THF's **(II-2)**. This reaction was completed within 30 min.

Zinc mediated reductive elimination of the crude product led to the alkenyl-acetal-alcohol **(II-8)** in 74% overall yield from the pyranoside alkene **(II-4)**.

Scheme II-2



(II-5) **(II-6)** **(II-7)** **(II-4)**

(II-2) **(II-8)**

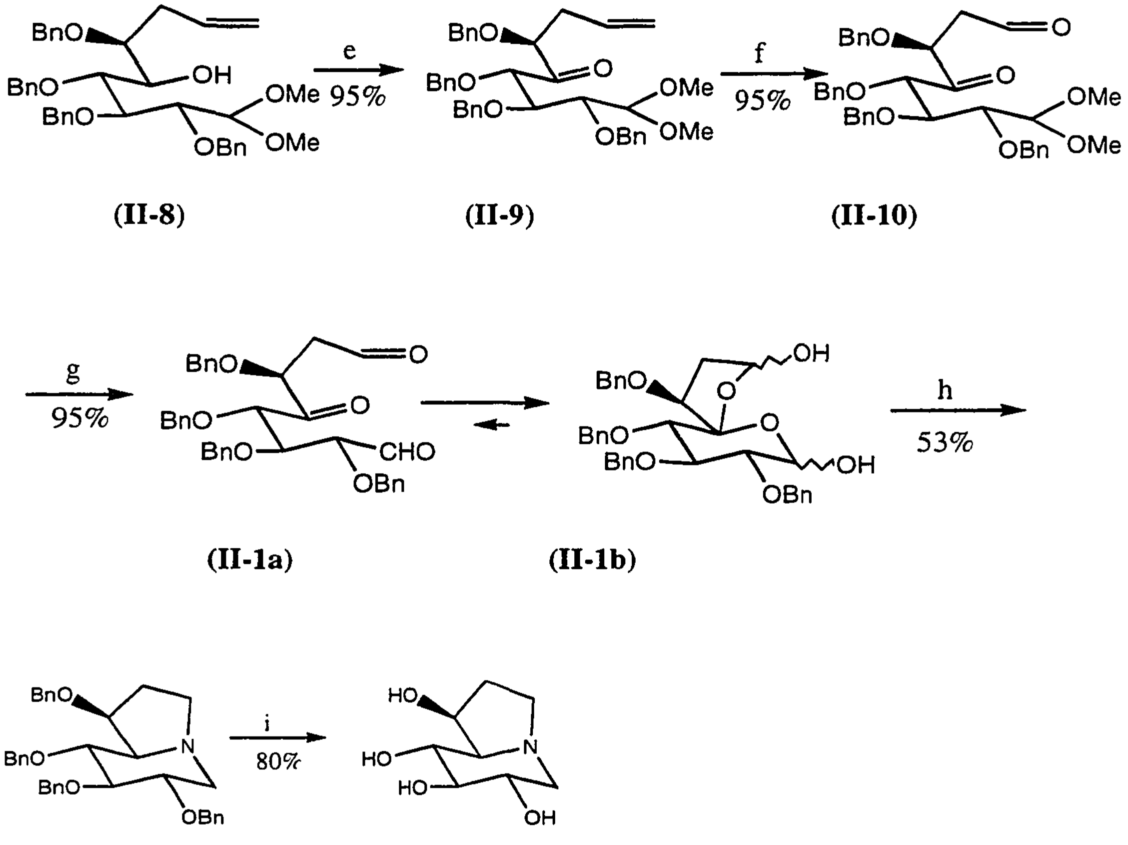
Key: (a). CH_2=$CHCH_2Br$, Sn, CH_3CN : H_2O = 10 : 1; b). NaH, BnBr, Bu_4NI, DMF; c). IDCP, MeOH, CH_2Cl_2; d). activated Zn, 95% EtOH;

The conversion of **(II-8)** to the requisite tricarbonyl compound **(II-1)** was achieved in 86 % via a three-step sequence of reactions: alcohol oxidation using the Swern's procedure to give the ketone **(II-9)**, ozonolysis of the alkene **(II-9)**, and acetal hydrolysis of the resulting keto aldehyde **(II-10)**. The product **(II-1)** did not show any aldehyde signals in the ^{1}H-NMR. Instead signals at 5.17-5.53 ppm (m, 2H) corresponding to acetal protons, were observed. No signals for carbonyl carbons were observed in the ^{13}C NMR, but resonaces at 93.70 ppm, 93.92 ppm, 97.33 ppm, 98.14 ppm, 103.52 ppm, and 103.67 ppm, matching acetal carbons, were present. This data is consistent with the acetal structure **(II-1b).** The elemental analysis and mass spectrum was also consistent with **(II-1b).** (Scheme II-3)

Treatment of **(II-1b)** in anhydrous methanol, with 1.5 equivalents of ammonium formate and 30 equivalents of sodium cyanoborohydride, over 24 h, led to the formation of a major compound **(II-11)** in 53% yield, after chromatography[41]. Within the limits of NMR detection, less than 5% of the C8a epimer was observed. An intractable mixture of several minor, highly polar components (~20%) was obtained. The structure of **(II-11)** was confirmed by 2D COSY analysis. Hydrogenolysis of **(II-11)** gave a product which was essentially identical with natural castanospermine **(I-1),** and samples from other synthetic studies (tlc, mp, NMR, α_D)[8,12,29,42]. The overall yield of **(I-1)** from methyl 4,6,-O-benzylid

ene–α–D-glucopyranoside was 18 % over 12 steps, which represents one of the most efficient syntheses of castanospermine **(I-1).** (Scheme II-4)

Scheme II-3



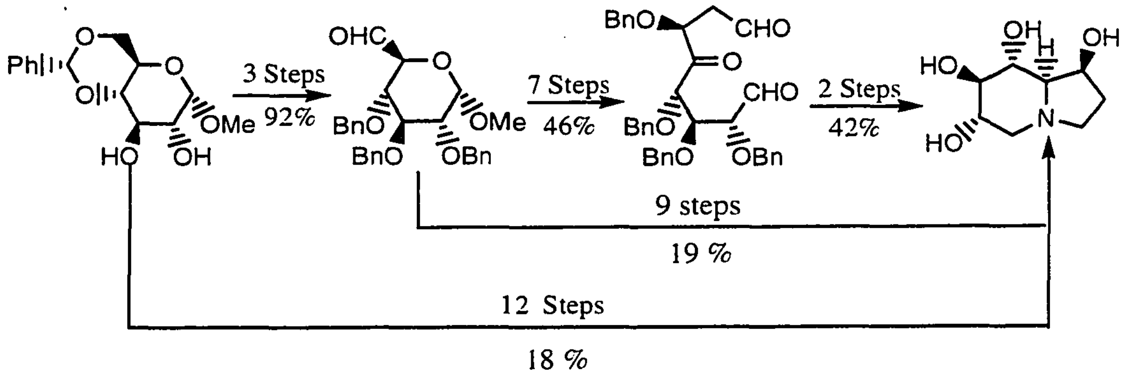
(II-8) (II-9) (II-10)

(II-1a) (II-1b)

(II-11) (I-1)

Key: e). $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; f). O_3, CH_2Cl_2 : MeOH = 5 : 1; g). HCl, H_2O, THF; h). $HCOONH_4$, $NaBH_3CN$, MeOH; i). Pd/C 10%, HCOOH, MeOH;

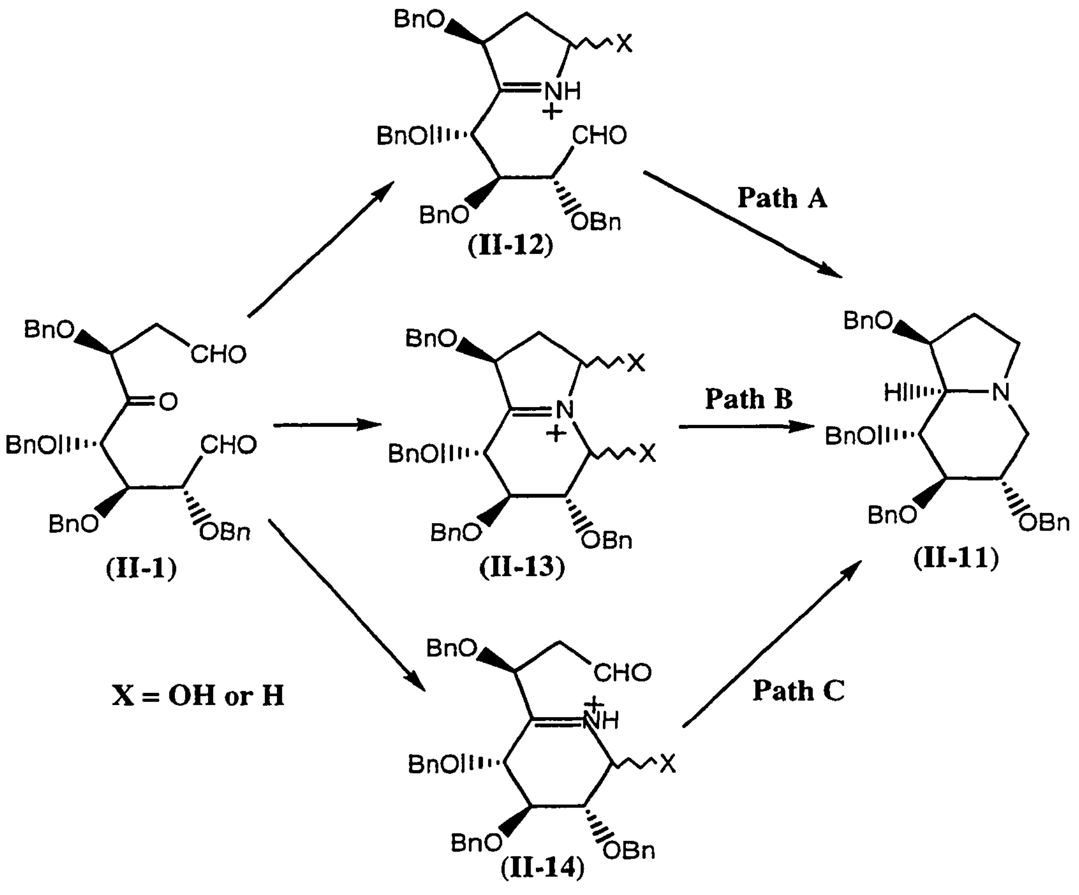
Scheme II-4



II.3 Mechanistic Studies

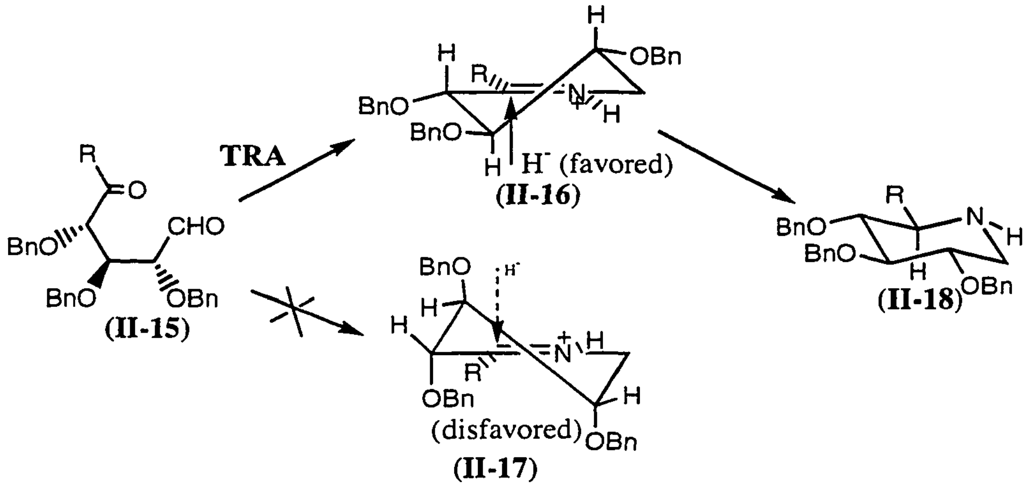
The preponderance of monoamination vs. di- and tri- aminated products suggests that initial amination on **(II-1)** occurs at one of the carbonyl groups (more likely one or other of the two aldehydes), and the resulting carbinolamine or amine undergoes sequential intramolecular reactions with the remaining carbonyl groups, at a faster rate than a second or third intermolecular amination. According to this mechanism, stereoselectivity will be determined by in the hydride addition to monocyclic or bicyclic iminium ions **(II-12)**, **(II-13)** or **(II-14)** (Scheme II-5)[41]. The facial biases of **(II-12)**, **(II-13)** and **(II-14)** may be opposed, in which case the overall stereoselectivity will be poor if there is no preferred product determining pathway. If all three have the same stereochemical bias, the irrelative rates of reduction are inconsequential, and prediction of the stereochemical result is clear-cut. This appears to be situation for the case at hand.

Scheme II-5

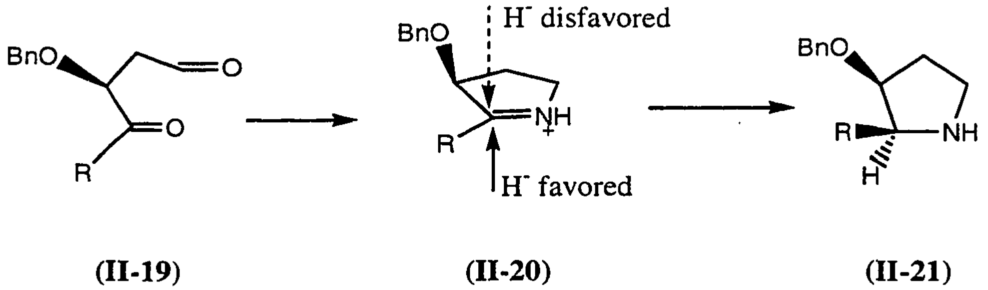


Hydride reduction on **(II-12)**, **(II-13)** and **(II-14)** is expected to occur with high selectivity in the same sense. This conclusion follows from the proposed model for the addition of nucleophiles to cyclic iminium ions[43], and results of the double reductive amination of closely related systems (Scheme II-6a / II-6b)[29,33,41]. Thus, reduction of the five membered iminium ion like **(II-12)** is expected to occur anti to the α-benzyloxy substituent to afford pyrrolidine **(II-21)** (Scheme II-6b). Nucleophilic addition to cyclic six-membered iminium ions like **(II-14)** is expected to occur via the half chair in which the benzyloxy substituents are in pseudo-equatorial positions. Addition of hydride in an axial trajectory to give **(II-18)** is favored because this results in a chair-like transition state geometry (Scheme II-6a)[43]. Extension of this model to the bicyclic species **(II-13)** would give the same facial preference.

Scheme II-6a



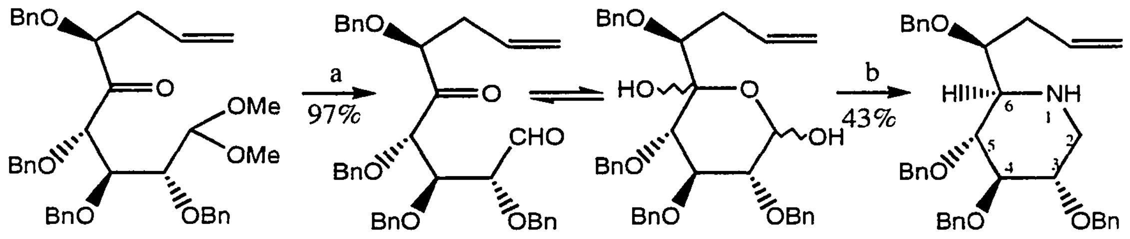
Scheme II-6b



In order to get a clearer picture of the reaction mechanism, attempts were made to isolate the intermediate reduction products. However these were not successful. Reduction in the amount of sodium cyanoborohydride or shorter reaction times led to varying amounts of the final product and a complex mixture of more polar components, which were not separable. Next, the double reductive aminations of the five and six membered ring were separately examined, on the assumption that the yield and stereoselectivity of these reactions would provide mechanistic insight.

Hydrolysis of the previously described keto acetal **(II-9)** with 9M HCl gave a mixture of keto-aldehyde **(II-22a)** and acetals **(II-22b).** Treatment of the mixture under the TRA conditions gave a single product **(II-23)** in 43% yield. The configuration of C8a was determined by NMR (1D & 2D), and was identical with that of C8a in castanospermine. (Scheme II-7)

Scheme II-7

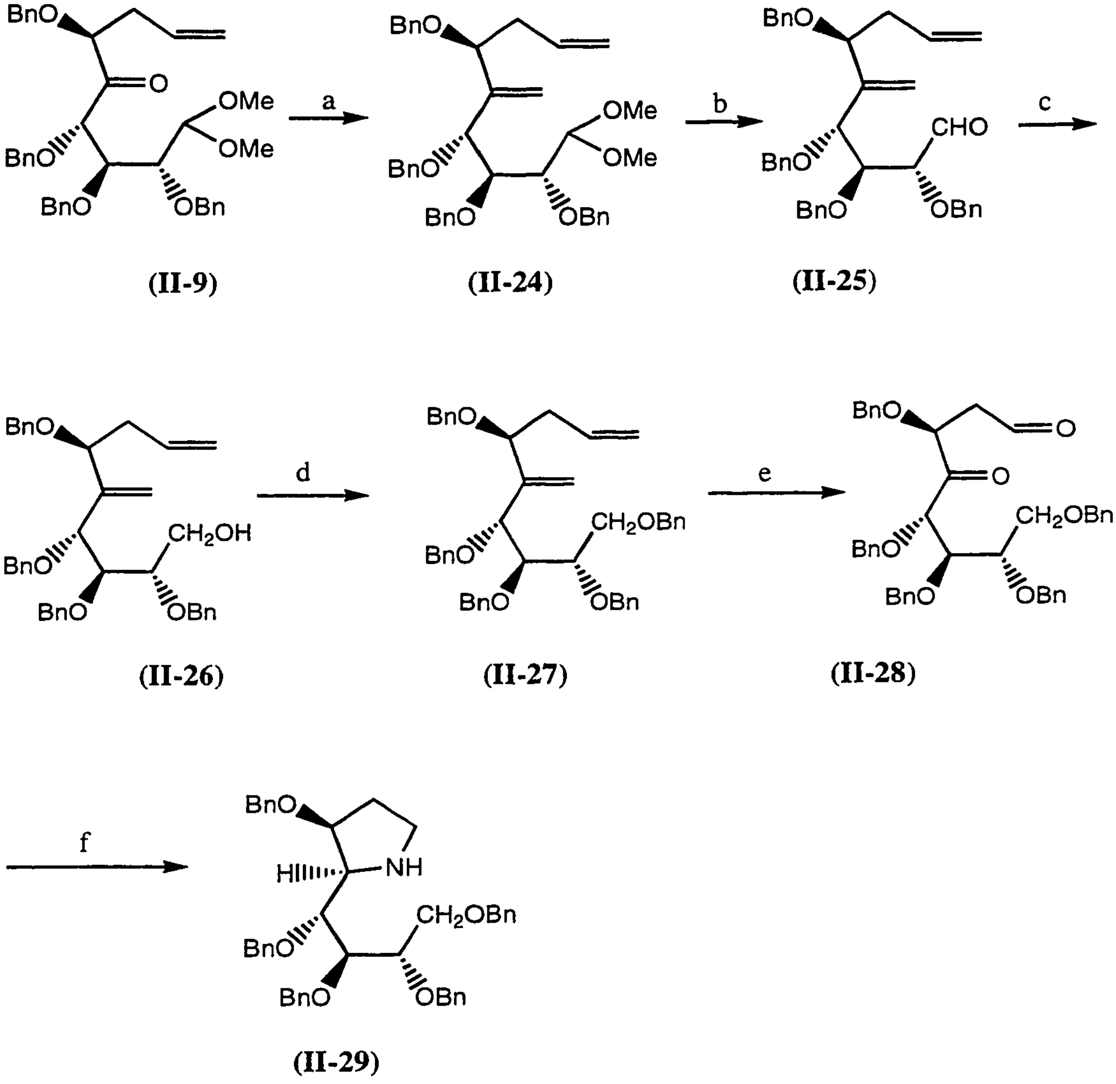


(II-9) **(II-22a)** **(II-22b)** **(II-23)**

Key: (a) THF—9M HCl; (b) 1.5 (eq) NH_4HCO_2, 30 (eq) $NaCNBH_3$, MeOH.

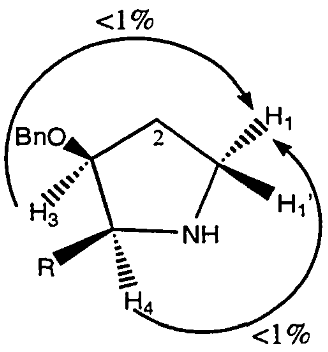
The keto-aldehyde **(II-28)** was also prepared from keto–alkene **(II-9).** Wittg methylenation of compound **(II-9)** provided to diene **(II-24)**, Hydrolysis of **(II-24),** followed by aldehyde reduction and benzylation of the resulting alcohol, provided diene ether **(II-27).** Ozonolysis of **(II-27)** gave the keto–aldehyde **(II-28).** Treatment of **(II-28)** under reductive amination conditions gave a mixture of two compounds **(II-29)** and an unidentified mixture of lower polarity, in 20 % and 15 % yield respectively. The stereochemistry of **(II-29)** was assigned by COSY, and NOESY NMR. nOe's between H_3 and H_4 and the same H_1 proton indicated that all three protons are cis and that **(II-29)** was the pyrrolidine with the same C8a stereochemistry as castanospermine. (fig II-1)

Scheme II-8



Key: (a). $Ph_3P=CH_2$; (b) THF—9M HCl; (c) $NaBH_4$, EtOH; (d) NaH, BnBr, n-Bu_4NI; (e) O_3, CH_2Cl_2, -78 °C then Ph_3P; (f) 1.5 (eq) NH_4HCO_2, 30 (eq) $NaCNBH_3$, MeOH.

Figure II-1



That the stereochemistry of both the piperidine and pyrrolidine products is the same as in product of the TRA, does not distinguish any of the three pathways. However the much lower yield of the pyrrolidine product suggests that path **A** is a minor pathway in the TRA.(Scheme II-5)

II.4 Experimental

II.4.1 General Procedures

Proton and Carbon Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C-NMR) were recorded on a GE, QE 300 instrument or Varian Unity Plus 500 MHz instruments in C_6D_6 or $CDCl_3$ solutions, with $CHCl_3$ or C_6H_6 respectively as internal standard. Chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane; coupling constants (J) are given in Hertz (Hz). The splitting patterns are designated s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triplet), q (quartet), m (multiplet), and br (broad). Hydroxyl protons were identified by exchanged with deuterium oxide. Elemental analysis were performed by Schwarzkopf Microanalysis Laboratory. High Resolution Mass Spectrometry (HRMS) was carried out by the Mass Spectrometry

Laboratory, University of Illinois at Urbana-champaign. Optical rotations were determined on a Rudolph Research AUTOPOL III automatic polarimeter. Melting points are reported uncorrected.

The progress of all reactions was monitored by thin layer chromatography (tlc) on aluminum sheets precoated with silica gel 60 (HF-254, E. Merck) to a thickness of 0.25 mm. Chromatograms were visualized under ultraviolet light, or sprayed with a solution of ammonium molybdate VI tetrahydrate (12.5g) and cerium (IV) sulfate tetrahydrate (5.0g) in 10% aqueous sulfuric acid (500mL) and charred by heating on a hot plate. Flash chromatography was performed using Kieselgel 60 (230-400 mesh) and unless otherwise stated employed a stepwise solvent polarity gradient of the solvent mixture reported for tlc. Solvent mixtures of ethyl acetate (EtOAc) and petroleum ether (P.E) bp. 35 – 60 °C, were commonly used.

Solvents were reagent grade and were used without further purification, unless otherwise stated. Anhydrous diethyl ether and THF were distilled under N_2 from sodium and potassium benzophenone ketyl. Anhydrous dichloromethane (CH_2Cl_2) was distilled from phosphorous pentaoxide (P_2O_5). Anhydrous triethylamine (Et_3N) and dimethylformamide (DMF) were distilled from calcium hydride. Benzene and toluene were dried by azeotropic removal of water.

II.4.2 Benzylation of Alcohols

Tetra-butylammonium iodide (0.1 mol / mol of alcohol) and sodium hydride (1.5 mol / mol of alcohol, 60% suspension in mineral oil), were added to a solution of the alcohol in dry DMF (5 mL / mmol of alcohol) at 0°C. After stirring at this temperature for 20 min, benzyl bromide (1.2 mmol / mmol of alcohol) was added. The reaction mixture was warmed to rt, and stirred for an additional one hour. The mixture was recooled to 0°C, carefully quenched with methanol, and diluted with water. The resulting suspension was extracted with ether (x 3), the combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography.

II.4.3 Iodoetherification of Pyranoside Alkenes

To a stirred solution of the pyranoside alkene in dry CH_2Cl_2 (10 mL / mmol of alkene) and the desired nucleophile (water, methanol, or 4-methoxybenzyl alcohol, 3.0 mmol / mmol of alkene), was added iodonium dicollidine perchlorate[35] (IDCP, 1.2 mmol / mmol of alkene). The progress of the reaction was followed by tlc. Upon completion (about 20 min.), the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution, and extracted with ether (x 3). The combined organic extract was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography.

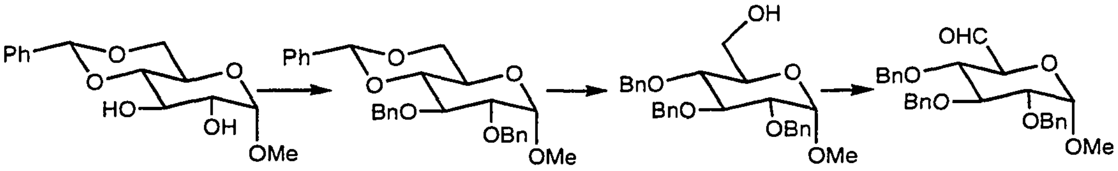
II.4.4 Reductive Elimination of Iodo THF's

A mixture of iodo-THF's and freshly activated Zn dust (10 mmol / mmol of iodo-THF's) in 95% EtOH (10 mL / mmol of iodo-THF's) was heated at reflux for 30 min. The reaction mixture was cooled to rt and filtered through a short column of celite. The filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography.

II.4.5 Swern's Oxidation[44] of Alcohols

DMSO (3.0 mmol / mmol of alcohol) was slowly added to a solution of oxalyl chloride (2.5 mmol / mmol of alcohol) in anhydrous CH_2Cl_2 (3 mL / mmol of alcohol) at –78 °C. The reaction mixture was stirred at this temperature for 20 min, at which time a solution of alcohol in anhydrous CH_2Cl_2 (5 mL / mmol of alcohol) was slowly introduced. Stirring was continued at this temperature for an additional 20 min, then Et_3N (5.0 mmol / mmol of alcohol) was added to the solution. The reaction mixture was warmed to rt, then diluted with ether (15 mL / mmol of alcohol). The resulting suspension was washed with saturated $NaHCO_3$, and the aqueous layer extracted with ether (3 x). The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography.

II.4.6 Preparation of Pyranoside Aldehyde (II-5)[38]



(II-5)

The known methyl 4,6,-O-benzylidine-α–D-glucopyranoside[45] (10.0 g, 35.5 mmol) from methyl α–D-glucopyranoside in one step was benzylated according to the general procedure for benzylation **(II.4.2)**. Methyl 4, 6,-O-benzylidine-2,3-di-O-benzyl–α–D-glucopyranoside (15.4 g, 94%) was obtained; $R_f = 0.70$ (EtOAc : PE = 20 : 80); ^{1}H

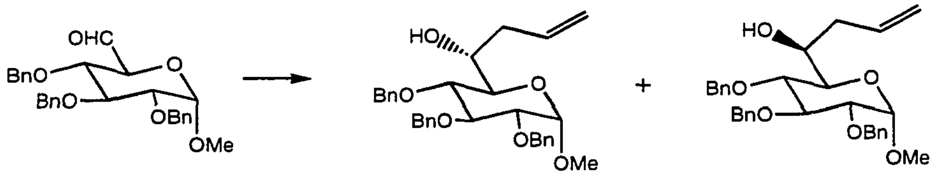
NMR ($CDCl_3$) δ 3.41 (s, 3H), 3.55 (dd, 1H, J = 3.6, 9.2 Hz), 3.61 (t, 1H, J = 9.2 Hz), 3.71 (t, 1H, J = 10.2 Hz), 3.85 (m, 1H), 4.05 (t, 1H, J = 9.2 Hz), 4.27 (dd, 1H, J = 4.8, 9.2 Hz), 4.60 (d, 1H, J = 3.6 Hz), 4.78 (ABq, Δδ = 0.16 ppm, 2H, J = 12.4 Hz), 4.88 (ABq, Δδ = 0.10 ppm, 2H, J = 11.1 Hz), 5.56 (s, 1H), 7.37 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 55.53, 62.51, 69.23, 73.93, 75.48, 78.76, 79.37, 82.30, 99.35, 101.38, 126.12, 127.64, 127.98, 128.08, 128.17, 128.28, 128.37, 128.51, 128.96, 137.49, 138.23, 138.81.

Methyl 4, 6,-O-benzylidene-2,3-di-O-benzyl–α–D-glucopyranoside (15.4 g, 33.2 mmol) in anhydrous CH_2Cl_2 (60 mL) was added to a suspension of lithium aluminum hydride (1.51 g, 39.8 mmol) in anhydrous 1 : 1 CH_2Cl_2–diethyl ether (60 mL). An ethereal solution of aluminum trichloride (5.18 g, 39.8 mmol) was added to the resulting suspension such that the final ratio of CH_2Cl_2–diethyl ether was 1 : 3 (v / v). The reaction mixture was heated at reflux for 40 h, under an argon atmosphere. The reaction was quenched by adding cold water, and the mixture extracted with ether and chloroform. The combined organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography gave methyl 2,3,4-tri-O-benzyl–α–D-glucopyranoside (15.1 g, 98 %). R_f = 0.30 (EtOAc : PE = 20 : 80); ^1H NMR ($CDCl_3$) δ 1.76 (br, 1H), 3.37 (s, 3H), 3.48 (m, 2H), 3.67 (m, 3H), 3.96 (t, 1H, J = 10.2 Hz), 4.53 (d, 1H, J = 3.6 Hz), 4.68 (ABq, Δδ = 0.18 ppm, 2H, J = 12.0 Hz), 4.74 (ABq, Δδ = 0.25 ppm, 2H, J = 11.7 Hz), 4.87 (ABq, Δδ = 0.16 ppm, 2H, J = 11.1 Hz), 7.24 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 55.31, 62.02, 70.92, 73.53, 75.14, 75.83, 77.66, 80.26, 82.11, 98.35, 127.70, 127.96, 128.06, 128.10, 128.21, 128.51, 128.59, 138.34, 138.97.

Application of the general procedure for Swern's oxidation to the alcohol from the previous step (5.8 g, mmol) gave aldehyde **(II-5)** in quantitative yield. R_f = 0.30

(EtOAc : PE = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 3.39, 3.41 (s, 3H), 3.49 (m, 2H), 3.78 (m, 1H), 4.00 (t, 1H, J = 9.3 Hz), 4.61 – 5.01, 9.68 (m, 8H), 7.34 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 56.09, 56.52, 63.93, 73.52, 74.21, 74.31, 74.94, 75.81, 75.89, 75.97, 76.36, 76.46, 77.94, 78.02, 78.30, 78.56, 78.96, 79.33, 80.07, 80.58, 80.71, 82.46, 82.56, 82.83, 98.84, 98.93, 99.02, 99.11, 128.13 – 129.12 (several lines), 138.47, 138.68, 138.84, 139.08, 139.30, 207.63.

II.4.7 Allylation of Pyranoside Aldehyde (II-5)



1 : 9

(II-5) **(II-6)** **(II-7)**

Allylation with Sn/Allyl Bromide

Tin powder (121 mg, 1.02mmol, 100 mesh) and allyl bromide (0.136 mL, 1.53 mmol) was added to a solution of aldehyde **(II-5)** (236 mg, 0.51mmol) in a mixture of 10:1 CH_3CN : H_2O (11 mL). The reaction was placed in an ultrasonic bath for 16 h. 6M NaOH was then added to the reaction mixture to pH = 8, and the resulting slurry filtered through a celite pad. The filtrate was extracted with ether (3 x 30 mL). The combined organic phase was washed with brine (30 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography afforded a major component **(II-7)** (193 mg, 75%) and a minor component **(II-6)** (20 mg, 8%).

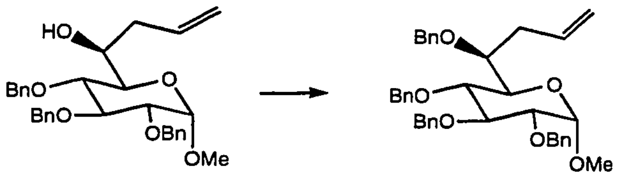
Allylation with Allylmagnesium Bromide

To a solution of the aldehyde **(II-5)** (236 mg, 0.51mmol) in anhydrous THF (60 mL) was added dropwise allylmagnesium bromide (1M in THF, 38.7 mL, 38.7 mmol) in a period of 20 min at 0 °C. After an additional 30 min, saturated aqueous NH_4Cl (100 mL) was added. The mixture was extracted with ether (3 X). The combined organic phase was washed with brine, dried (Na_2SO4) and concentrated *in vacuo*. The residue was purified by flash chromatography to afforded a mixture of **(II-6)** and **(II-7)** (5.10 g, 78%, 1 : 1).

For **(II-7)**: R_f = 0.70 (EtOAc : P.E = 40 : 60); ^{1}H NMR ($CDCl_3$) δ 2.23 (m, 1H), 2.36 (m, 1H), 3.32 (s, 3H), 3.46 (dd, 1H, J = 3.6, 9.6 Hz), 3.50 (d, 1H, J = 9.3 Hz), 3.65 (t, 1H, J = 9.3 Hz), 3.86 (m, 1H), 3.95 (t, 1H, J = 9.3 Hz), 4.55 (d, 1H, J = 3.6 Hz), 4.69 (ABq, Δδ = 0.15 ppm, 2H, J = 12.0 Hz), 4.76 (ABq, Δδ = 0.22 ppm, 2H, J = 10.8 Hz), 4.87 (ABq, Δδ = 0.15 ppm, 2H, J = 10.8 Hz), 5.07 (m, 2H), 5.78 (m, 1H), 7.25 –7.32 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 38.83, 55.48, 68.12, 71.75, 73.63, 75.33, 75.89, 77.83, 80.02, 82.25, 98.56, 118.00, 127.74, 127.93, 128.10, 128.31, 128.62, 135.00, 138.34, 138.53, 138.98

For **(II-6)**: R_f = 0.65 (EtOAc : P.E = 40 : 60); ^{1}H NMR ($CDCl_3$) δ 2.20 (m, 2H), 2.28 (br, 1H), 3.31 (s, 3H), 3.43 (m, 2H), 3.62 (dd, 1H, J = 4.5, 9.9 Hz), 3.77 (m, 1H), 3.96 (t, 1H, J = 9.3 Hz), 4.50 (d, 1H, J = 3.6 Hz), 4.65 (ABq, Δδ = 0.13 ppm, 2H, J = 11.7 Hz), 4.74 (ABq, Δδ = 0.32 ppm, 2H, J = 11.1 Hz), 4.84 (ABq, Δδ = 0.22 ppm, 2H, J = 10.8 Hz), 5.00 (m, 2H), 5.79 (m, 1H), 7.15 –7.36 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 36.74, 55.40, 71.65, 71.84, 73.38, 74.81, 75.75, 79.79, 80.38, 82.45, 97.96, 117.39, 127.73-128.51 (several lines), 135.27, 137.88, 138.20, 138.73.

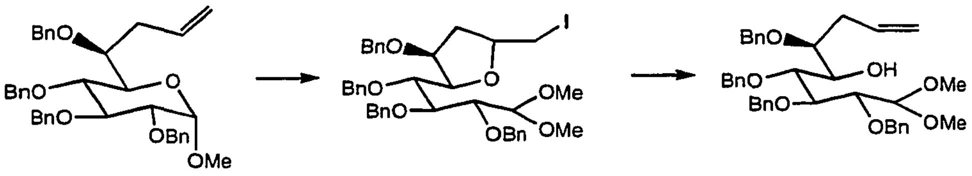
II.4.8 Preparation of Pyranoside Alkene (II-4)



(II-7) **(II-4)**

The major product **(II-7)** from the previous step (4.8 g, 9.5 mmol) was benzylated according to the general procedure for benzylation of alcohol **(II.4.2)**. Compound **(II-4)** (5.50 g, 97%) was obtained; $[\alpha]_D$ –20.1 (c = 5.7, $CHCl_3$); R_f = 0.80 (EtOAc : PE = 20 : 80); ^1H NMR ($CDCl_3$) δ 2.58 (m, 2H), 3.41 (s, 3H), 3.59 (dd, 1H, J = 3.6, 9.9 Hz), 3.72 (m, 2H), 3.89 (dd, 1H, J = 5.4, 8.4 Hz), 4.34 (d, 1H, J = 11.1 Hz), 4.38 (d, 1H, J = 11.7 Hz), 4.69 (m, 2H), 4.81 (ABq, $\Delta\delta$ = 0.02 ppm, 2H, J = 10.5 Hz), 4.90 (d, 1H, J = 11.4 Hz), 5.01 (d, 1H, J = 10.5 Hz), 5.14 (m, 2H), 5.86 (m, 1H), 7.34 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 34.51, 55.78, 71.09, 71.99, 73.58, 74.72, 75.71, 75.99, 80.06, 82.62, 98.55, 117.78, 127.63 - 128.55 (several lines), 134.79, 138.21, 138.35, 138.79.

II.4.9 Preparation of Hydroxy Alkene (II-8)

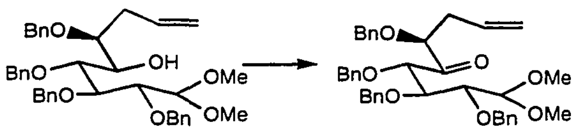


(II-4) **(II-2)** **(II-8)**

Pyranoside alkene **(II-4)** (3.21 g, 6.9 mmol) was treated according to the general procedure for iodoetherification of alkenes **(II.4.3)** using MeOH as the nucleophile. A mixture of products **(II-2)** was obtained. For characterization purposes, a sample of this material was purified by flash chromatography; R_f = 0.50 (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 1.29, 1.66, 2.19, 2.43 (m, 2H), 3.21 (m, 2H), 3.27, 3.31, 3.46, 3.51 (s, 6H), 3.95 (m, 3H), 4.21 – 4.38 (m, 5H), 4.50 – 4.92 (m, 7H), 7.34 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 10.05, 12.52, 35.64, 37.86, 54.52, 54.65, 56.13, 56.27, 70.96, 71.08, 74.11, 74.43, 74.87, 74.96, 75.36, 76.34, 76.67, 78.63, 79.12, 80.11, 81.73, 82.53, 83.62, 85.67, 106.13, 106.26, 127.31 – 128.48 (several lines), 138.01, 138.22, 138.87, 139.10, 139.39, 139.51.

The crude product **(II-2)** from last step was treated according to the general procedure for reductive elimination **(II.4.4)**. This provided hydroxyl alkene **(II-8)** (2.1 g, 74%). $[\alpha]_D$ +26.8 (c = 4.1, $CHCl_3$); R_f = 0.50 (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.55 (m, 2H), 3.37 (s, 3H), 3.48 (s, 3H), 3.55 (m, 1H), 3.72 (m, 2H), 3.87 (m, 1H), 4.32 (d, 1H, J = 11.1 Hz), 4.37 (d, 1H, J = 11.7 Hz), 4.67 (m, 3H), 4.79 (ABq, $\Delta\delta$ = 0.02 ppm, J = 10.5 Hz, 2H), 4.89 (d, 1H, J = 11.4 Hz), 4.99 (d, 1H, J = 10.5 Hz), 5.13 (m, 2H), 5.81 (m, 1H), 7.32 (m, 20H); ^{13}C NMR (CDCl$_3$) δ 34.53, 55.80, 71.11, 72.03, 73.61, 74.75, 75.75, 76.02, 80.09, 82.65, 98.58, 117.80, 127.71 - 128.64 (several lines), 134.82, 138.20, 138.33, 138.81; Anal calcd for $C_{39}H_{46}O_7$: C, 74.74; H, 7.40. found: C, 74.35; H, 7.43.

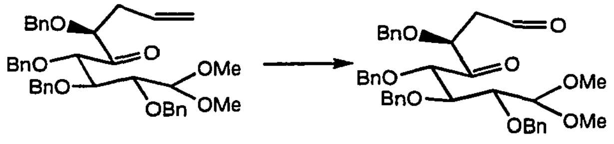
II.4.10 Preparation of Ketone (II-9)



(II-8) **(II-9)**

Treatment of the hydroxyl alkene **(II-8)** (2.1 g, 3.4 mmol) according to the general procedure for Swern's oxidation (**II.4.6**) afforded ketone **(II-9)** (2.0 g, 95%). R_f = 0.6 (EtOAc : P.E = 20 : 80); $[\alpha]_D$ −16.8 (c = 4.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 2.25 (m, 1H), 2.40 (m, 1H), 3.33 (s, 3H), 3.40 (s, 3H), 3.80 (dd, 1H, J = 3.9, 6.3 Hz), 4.10 (m, 2H), 4.27 (d, 1H, J = 5.7 Hz), 4.36 (m, 2H), 4.50 (m, 2H), 4.66 (m, 4H), 4.74 (d, 1H, J = 11.1 Hz), 4.98 (m, 2H), 5.72 (m, 1H), 7.25 (m, 20H); ^{13}C NMR (CDCl$_3$) δ 36.47, 54.42, 55.82, 71.94, 73.41, 74.32, 74.83, 77.86, 79.74, 80.76, 81.68, 105.52, 117.59, 127.52-128.75 (several lines), 133.93, 137.85, 138.15, 138.35, 138.94, 207.87.

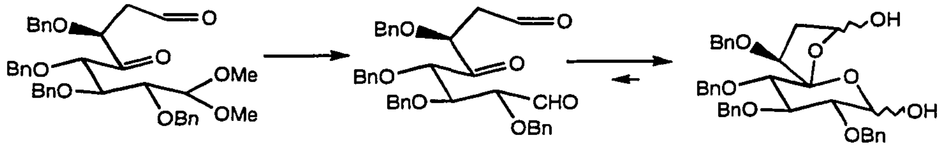
II.4.11 Preparation of Keto Aldehyde (II-10)



(II-9) **(II-10)**

O_3 was bubbled at -78 °C, through a solution of keto-alkene **(II-9)** (1.83 g, 2.94 mmol) in a mixture of CH_2Cl_2 (15 mL) and MeOH (3 mL). The reaction was allowed to proceed until tlc indicated complete disappearance of the starting material. The reaction vessel then was purged with argon, and the reaction mixture warmed to rt. Methanol (12 mL) and Ph_3P (1.2 g, 4.6 mmol) were added and stirring continued under an argon atmosphere for one hour. Concentration of the reaction mixture under reduced pressure, followed by flash chromatography of the residual slurry, afforded the keto-aldehyde **(II-10)** (1.73 g, 95%). $R_f = 0.35$ (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.45 (ddd, 1H, J = 2.1, 8.4, 14 Hz), 2.61 (dd, 1H, J = 3.6, 14 Hz), 3.38 (s, 3H), 3.43 (s, 3H), 3.82 (dd, 1H, J = 4.5, 5.7 Hz), 4.15 (m, 2H), 4.31 (d, 1H, J = 5.7 Hz), 4.35 (d, 1H, J = 11.4 Hz), 4.51-4.82 (m, 8H), 7.26 (m, 20H), 9.41 (d, 1H, J = 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 45.23, 54.91, 55.97, 72.62, 73.78, 74.38, 75.27, 77.79, 78.01, 80.04, 81.01, 105.77, 127.70-128.72 (several lines), 137.52, 137.70, 138.08, 138.76, 199.37, 208.07.

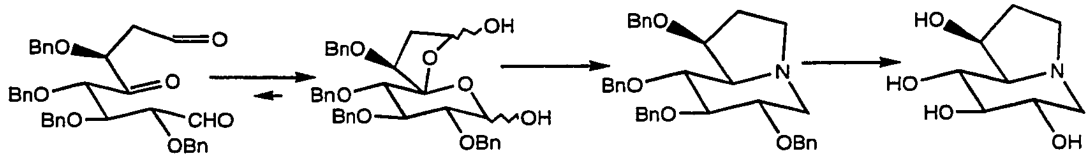
II.4.12 Preparation of Tricarbonyl Derivative (II-1)



(II-10) **(II-1a)** **(II-1b)**

9M HCl (15 mL) was added to a solution of the keto-aldehyde **(II-10)** (1.73 g, 2.78 mmol) in THF (45 mL). The reaction mixture was stirred at rt for one hour, then carefully neutralized by addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with ether (3 x 50 mL) and the combined organic phase was washed with brine (50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the semisolid residue afforded **(II-1)** as an amorphous, white solid (1.66 g, 95 %). Recrystallization from EtOAc-P.E afforded white needles (0.70 g, 40 %). Flash column chromatography of the mother liquor afforded a second crop of crystals (0.72 g, 41 %). $R_f = 0.3$ (EtOAc : P.E = 30 : 70); mp: 147-148 °C; $[\alpha]_D$ +16.5 (c = 1.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.99, 2.13, 2.39 (all m, 2H), 3.56 (m, 2H), 3.90 (m, 2H), 4.18-4.50 (m, 4H), 4.70-5.03 (m, 4H), 5.17-5.53 (m, 2H), 7.25 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 37.40, 37.75, 72.42, 74.85, 75.34, 75.42, 75.86, 75.97, 76.72, 78.13, 78.18, 82.01, 82.15, 83.71, 93.70, 93.92, 97.33, 98.14, 103.52, 103.67, 127.65-128.68 (several lines), 137.51, 137.58, 138.03, 138.62, 138.74; M.S (CI) 598 $[(M- H_2O) + NH_4^+]$; Anal calcd for **(II-1b)** $C_{36}H_{38}O_8$: C, 72.22; H, 6.40. found: C, 71.96; H, 6.58.

II.4.13 Preparation of Tetra-O-benzyl Castanospermine (II-11) and Castanospermine (I-1)

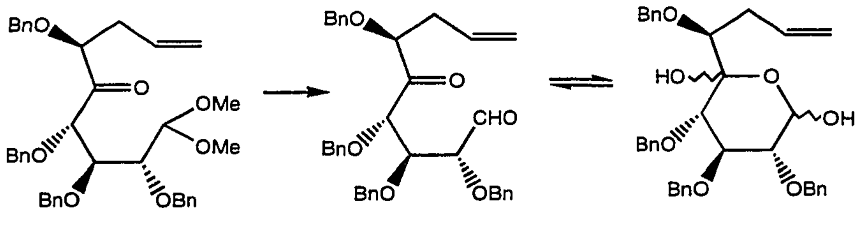


(II-1a) **(II-1b)** **(II-11)** **(I-1)**

Ammonium formate (7 mg, 0.1 mmol) and $NaCNBH_3$ (247 mg, 2.34 mmol) was added to a solution of **(II-1)** (47 mg, 0.078mmol) in anhydrous MeOH (15 mL). The reaction mixture was stirred for 24 h, at which time most of the solvent was removed *in vacuo*. The slurry was diluted with saturated aqueous Na_2CO_3, and the resulting suspension extracted with $CHCl_3$ (4 x 10 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), filtered evaporated in vacuo. Flash chromatography of the crude residue gave **(II-11)** (23 mg, 53%). R_f = 0.5 (EtOAc : toluene = 15 : 85); $[\alpha]_D$ +31.6 (c = 1.0, $CHCl_3$) ^{1}H NMR (C_6D_6) δ 1.73 (m, 3H), 1.91 (t, 1H, J = 10.2 Hz), 2.00 (dd, 1H, J = 5.1, 9.6 Hz), 2.89 (m, 1H), 3.15 (dd, 1H, J = 4.8, 10.2 Hz), 3.68 (t, 1H, J = 8.7 Hz), 3.80 (m, 1H), 3.93 (m, 1H), 4.18 (t, 1H, J = 8.7 Hz), 4.20 (ABq, $\Delta\delta$ = 0.22 ppm, 2H, J = 11.7 Hz), 4.50 (ABq, $\Delta\delta$ = 0.05 ppm, 2H, J = 11.7 Hz), 4.94 (ABq, $\Delta\delta$ = 0.25 ppm, 2H, J = 11.7 Hz), 5.00 (ABq, $\Delta\delta$ = 0.16 ppm, 2H, J = 11.4 Hz), 7.23 (m, 20H); ^{13}C NMR (C_6D_6) d 31.18, 53.19, 55.31, 70.93, 72.43, 73.13, 74.87, 75.97, 78.61, 78.52, 80.22, 88.72, 127.60-128.88 (several lines), 139.46, 139.87, 140.36, 140.88; Anal. Calcd for $C_{36}H_{39}O_4N$: C, 78.66; H, 7.15; N, 2.55. Found: C, 78.45; H, 7.37; N, 2.49.

10% Pd/C (500 mg) was added to a solution of **(II-11)** (120 mg, 0.22 mmol) in MeOH (4 mL) under an argon atmosphere. HCOOH (1 mL) was added to the suspension, the mixture stirred for 2h, and then filtered through a pad of celite. The filter cake was washed several times with methanol, and the filtrate was concentrated *in vacuo*. The residual syrup was dissolved in ethanol and stirred with Amberlite IRA-(OH) ion exchange resin (500 mg) for 30 min. The mixture was filtered through celite and the filtrate concentrated in vacuo to give a semisolid residue (33 mg, 80%). Recrystallization from ethanol afforded castanospermine **(I-1)** (29 mg, 70%) white prisms: mp 202-208 °C (dec), Lit: 212-215 °C (dec); $[\alpha]_D$ +70.1 (c = 0.33, H_2O), Lit: $[\alpha]_D$ +79.7 (c = 0.93, H_2O); R_f = 0.25 (MeOH : $CHCl_3$ = 30: 70) ^1H NMR, ^{13}C NMR and tlc was identical with natural castanospermine. ^1H NMR (D_2O) δ 1.69 (m, 1H), 2.02 (dd, 1H, J = 4.5, 9.9 Hz), 2.05 (t, 1H, J = 10.8 Hz), 2.21 (dd, 1H, J = 9.6, 17.4 Hz), 2.32 (m, 1H), 3.07 (dt, 1H, J = 2.1, 9.6 Hz), 3.17 (dd, 1H, J = 5.1, 11.1 Hz), 3.30 (t, 1H, J = 9.0 Hz), 3.59 (t, 1H, J = 9.6 Hz), 3.61 (m, 1H), 4.40 (m, 1H); ^{13}C NMR (D_2O) δ 31.73, 50.56, 54.35, 67.96, 68.59, 69.08, 70.39, 78.00.

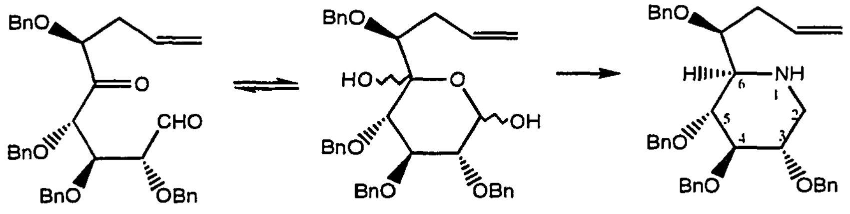
II.4.14 Synthesis of Keto Aldehyde (II-22)



(II-9) **(II-22a)** **(II-22b)**

Hydrolysis of compound **(II-9)** (0.165 g, 0.26 mmol) following procedure (II.4.12), afforded **(II-22)** (0.160 g, 97%). R_f = 0.40 (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.68 (m, 1H), 2.77 (m, 1H), 3.51 (m, 1H), 3.72 (m, 1H), 4.01 (m, 2H), 4.20, 4.31 (m, 1H), 4.43 (m, 1H), 4.60 (m, 3H), 4.80 (m, 3H), 4.99 – 5.46 (m, 3.5H), 5.78, 6.09 (m, 1H), 7.34 (m, 20H), 9.82 (s, 0.5H); ^{13}C NMR ($CDCl_3$) δ 33.10, 33.35, 35.41, 72.12, 72.23, 72.56, 73.40, 73.96, 74.28, 74.55, 74.75, 74.91, 75.90, 78.73, 78.85, 80.38, 80.50, 80.78, 80.95, 81.58, 82.00, 82.10, 82.21, 83.21, 93.30, 95.82, 98.52, 98.80, 117.14, 117.30, 117.68, 127.52, 127.63, 127.71, 127.76, 127.97, 128.07, 128.10, 128.24, 128.29, 128.41, 128.55, 128.59, 128.73, 128.86, 133.85, 136.25, 136.34, 136.60, 136.97, 137.13, 137.61, 138.13, 138.18, 138.30, 138.46, 138.50, 138.65, 200.27, 209.10.

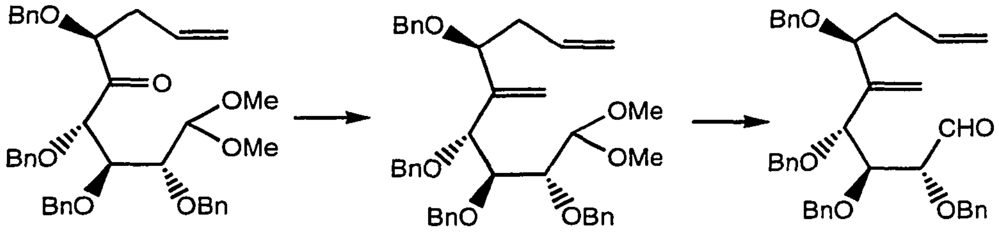
II.4.15 Double Reductive Amination of Keto Aldehyde (II-22)



(II-22a) **(II-22b)** **(II-23)**

Compound **(II-22)** (0.139 g, 0.22 mmol) was subjected to the standard reductive amination procedure (II.4.13). This experiment provided **(II-23)** (0.54 g, 43%). R_f = 0.50 (EtOAc : P.E = 20 : 80); ^{1}H NMR (C_6D_6) δ 1.20 (br, 1H, H-N), 2.38 (dd, 1H, J = 10.8, 13.5 Hz), 2.56 (m, 1H), 2.65 (d, 1H, J = 10.8 Hz), 2.75 (m, 1H), 3.54 (t, 1H, J = 9.0 Hz), 3.59 (t, 1H, J = 9.0 Hz), 3.91 (ddd, 1H, J = 1.2, 6.0, 8.7 Hz), 4.26 (ABq, Δδ = 0.34 ppm, 2H, J = 11.4 Hz), 4.43 (ABq, Δδ = 0.06 ppm, 2H, J = 11.7 Hz), 4.81 (ABq, Δδ = 0.48 ppm, 2H, J = 11.7 Hz), 4.96 (ABq, Δδ = 0.25 ppm, 2H, J = 11.1 Hz), 5.10 (m, 2H), 5.82 (m, 1H), 7.23 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 35.19, 48.11, 61.37, 71.79, 72.97, 74.99, 75.90, 76.32, 80.50, 81.82, 87.93, 117.55, 127.79 – 128.58 (several lines), 135.18, 138.68, 138.89, 139.10.

II.4.16 Synthesis of Dienol (II-25)

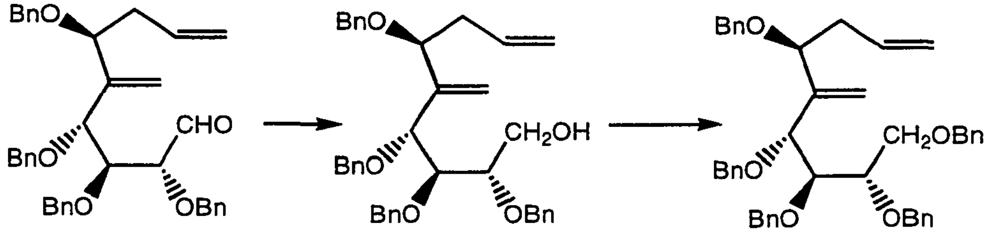


(II-9) **(II-24)** **(II-25)**

A Dean-stark trap was used to remove toluene (20 mL) from a suspension of $CH_3Ph_3P^+I^-$ (3.14 g, 7.7 mmol) in toluene (50 mL). The residual mixture was cooled to rt, and 1 M sodium bis(trimethylsilyl) amide (7.7 mL, 7.7 mmol) in hexane was added under an atmosphere of argon. The mixture was then stirred for one hour, then cooled to – 78 °C. The aldehyde **(II-9)** (1.92 g, 3.1 mmol) in dry toluene (20 mL) was slowly introduced over 15 min. The reaction mixture was warmed to rt, diluted with ether, filtered and evaporated *in vacuo*. Flash chromatography of the residual syrup provided diene **(II-24)** (1.15 g, 60 %). $R_f = 0.65$ (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.42 (m, 2H), 3.25 (s, 3H), 3.39 (s, 3H), 3.67 (t, 1H, J = 4.8 Hz), 3.84 (dd, 1H, J = 4.5, 6.0 Hz), 4.04 (dd, 1H, J = 3.9, 7.2 Hz), 4.24 (d, 1H, J = 6.3 Hz), 4.36 (d, 1H, J = 5.4 Hz), 4.64 (ABq, Δδ = 0.52 ppm, 2H, J = 11.4 Hz), 4.66 (ABq, Δδ = 0.08 ppm, 2H, J = 11.7 Hz), 4.67 (ABq, Δδ = 0.46 ppm, 2H, J = 11.7 Hz), 4.94 (ABq, Δδ = 0.33 ppm, 2H, J = 11.4 Hz), 5.15 (m, 2H), 5.41 (s, 1H), 5.54 (s, 1H), 5.92 (m, 1H), 7.34 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 39.85, 55.47, 55.65, 66.46, 70.82, 71.29, 74.09, 75.46, 78.77, 79.02, 79.99, 80.56, 105.58, 116.14, 116.77, 127.38, 127.46, 127.56, 127.64, 127.77, 127.86, 127.99, 128.04, 128.08, 128.20, 128.27, 128.32, 128.37, 128.51, 128.63, 135.40, 138.53, 138.75, 138.97, 139.03, 145.52.

Compound **(II-24)** (1.0 g, 1.6 mmol) was treated according to the hydrolysis procedure which was used in procedure (II.4.12). Compound **(II-25)** (0.58 g, 63 %) was obtained. R_f = 0.65 (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.42 (m, 2H), 3.89 (m, 2H), 3.94 (m, 1H), 4.26 (d, 1H, J = 3.3 Hz), 4.45 (ABq, Δδ = 0.16 ppm, 2H, J = 10.8 Hz), 4.48 (ABq, Δδ = 0.19 ppm, 2H, J = 11.7 Hz), 4.60 (ABq, Δδ = 0.21 ppm, 2H, J = 11.7 Hz), 4.70 (ABq, Δδ = 0.18 ppm, 2H, J = 11.7 Hz), 5.14 (m, 2H), 5.55 (s, 1H), 5.62 (s, 1H), 5.90 (m, 1H), 7.36 (m, 20H), 9.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 39.15, 70.90, 71.45, 73.14, 74.45, 77.54, 79.61, 80.85, 81.73, 116.12, 117.12, 127.64, 127.98, 128.10, 128.34, 128.38, 128.56, 134.86, 137.43, 137.71, 137.74, 138.44, 144.21, 200.07.

II.4.17 Synthesis of Penta-O-Benzyl Diene (II-27)



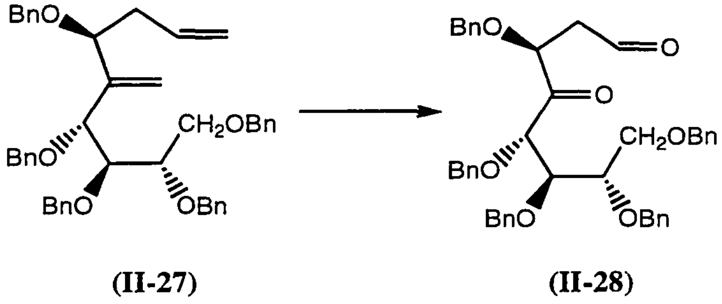
(II-25) **(II-26)** **(II-27)**

$NaBH_4$ (0.11 g, 2.81 mmol) was added to the solution of **(II-25)** (0.54 g, 0.94 mmol) in EtOH (30 mL) at rt. After stirring for one hour, the reaction was quenched by methanolic HCl and the pH of the solution adjusted to 7. The mixture was concentrated *in vacuo*. Flash chromatography afforded alcohol **(II-26)** (0.50 g, 91.5 %). R_f = 0.45 (EtOAc : P.E = 20 : 80); ^1H NMR ($CDCl_3$) δ 2.18 (m, 1H), 2.39 (m, 2H), 3.51 (m, 1H), 3.72 (m, 3H), 3.96 (t, 1H, J = 6.3 Hz), 4.14 (d, 1H, J = 1.8 Hz), 4.44 (ABq, $\Delta\delta$ = 0.25 ppm, 2H, J = 11.4 Hz), 4.50 (ABq, $\Delta\delta$ = 0.25 ppm, 2H, J = 11.7 Hz), 4.62 (ABq, $\Delta\delta$ = 0.07 ppm, 2H, J = 11.1 Hz), 4.71 (ABq, $\Delta\delta$ = 0.06 ppm, 2H, J = 10.8 Hz), 5.09 (m, 2H), 5.55 (s, 1H), 5.58 (s, 1H), 5.87 (m, 1H), 7.31 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 39.39, 61.85, 70.97, 71.26, 73.00, 74.97, 77.84, 79.55, 79.64, 80.46, 115.25, 117.06, 127.23, 127.68, 127.84, 127.94, 128.16, 128.42, 128.50, 135.01, 138.01, 138.30, 138.46, 138.55, 144.82.

The **(II-26)** (0.49 g, 0.58 mmol) was subjected to the general procedure for benzylation of alcohols **(II.4.2).** This provided penta-O-benzyl diene **(II-27)** (0.43 g, 76 %). R_f = 0.55 (EtOAc : P.E = 10 : 90); ^1H NMR ($CDCl_3$) δ 2.40 (t, 1H, J = 6.0 Hz), 3.39

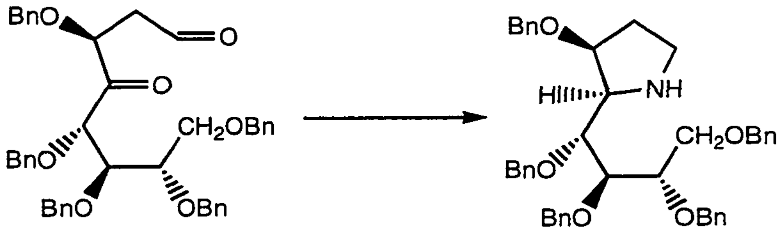
(dd, 1H, J = 4.8, 10.8 Hz), 3.60 (dd, 1H, J = 3.6, 10.8 Hz), 3.77 (t, 1H, J = 4.8 Hz), 3.87 (dd, 1H, J = 4.8, 6.0 Hz), 3.95 (t, 1H, J = 6.0 Hz), 4.17 (m, 1H), 4.31 (ABq, $\Delta\delta$ = 0.28 ppm, 2H, J = 12.0 Hz), 4.45 (ABq, $\Delta\delta$ = 0.33 ppm, 2H, J = 11.1 Hz), 4.51 (ABq, $\Delta\delta$ = 0.27 ppm, 2H, J = 11.4 Hz), 4.65 (ABq, $\Delta\delta$ = 0.13 ppm, 2H, J = 11.7 Hz), 4.75 (s, 2H), 5.08 (m, 2H), 5.54 (s, 1H), 5.55 (s, 1H), 5.89 (m, 1H), 7.32 (m, 25H); ^{13}C NMR ($CDCl_3$) δ 29.95, 39.55, 70.09, 70.91, 71.17, 73.10, 73.49, 75.24, 78.68, 79.33, 79.47, 80.06, 115.76, 116.91, 127.53, 127.62, 127.67, 127.81, 127.93, 128.04, 128.25, 128.35, 128.44, 135.18, 138.31, 138.40, 138.68, 138.72, 138.89, 145.04.

II.4.18 Synthesis of Keto Aldehyde (II-28)



The **(II-27)** (0.33 g, 0.5 mmol) was subjected to the general procedure for ozonolysis of alkene **(II.4.12)**. Keto aldehyde **(II-28)** (0.20 g, 61 %) was obtained. **(II-28)** R_f = 0.70 (EtOAc : P.E = 30 : 70); ^{1}H NMR ($CDCl_3$) δ 2.46 (m, 1H), 2.79 (dd. 1H, J = 3.3, 17.4 Hz), 3.59 (dd, 1H, J = 5.4, 10.2 Hz), 3.76 (dd, 1H, J = 4.2, 10.8 Hz), 4.00 (dd, 1H, J = 5.4, 9.3 Hz), 4.21 (dd, 1H, J = 4.2, 5.4 Hz), 4.35 (d, 1H, J = 3.9 Hz), 4.42 (ABq, $\Delta\delta$ = 0.24 ppm, 2H, J = 11.4 Hz), 4.47 (m, 5H), 4.70 (m, 4H), 7.35 (m, 25H), 9.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 44.95, 70.10, 72.61, 73.23, 73.41, 73.87, 75.00, 77.54, 77.80, 79.70, 81.85, 127.72, 127.82, 127.93, 127.97, 128.10, 128.20, 128.37, 128.42, 128.56, 128.67, 137.03, 137.36, 137.69, 138.19, 138.37, 198.88, 208.42.

II.4.19 Double Reductive Amination of Keto Aldehyde (II-28)



(II-28) **(II-29)**

The **(II-28)** (0.18 g, 0.27 mmol) was treated according to the standard triple reductive amination conditions (II.4.13). Two components, **(II-29)** (0.035 g, 20 %) and an inseparable mixture of lower polarity (R_f = 0.40 in EtOAc : P.E = 50 : 50; 0.023 g) were obtained after flash chromatography of the crude residue. **(II-29)** R_f = 0.45 (EtOAc : P.E = 50 : 50); ^1H NMR (C_6D_6) δ 1.08 (m, 1H), 1.55 (m, 1H), 1.62 (m, 1H), 3.27 (m, 1H), 3.35 (m, 1H), 3.44 (m, 1H), 3.56 (m, 1H), 3.67 (m, 1H), 3.79 (s, 2H), 3.89 (s, 2H), 4.04 (s, 2H), 4.13 (ABq, Δδ = 0.30 ppm, 2H, J = 12.0 Hz), 4.27 (ABq, Δδ = 0.19 ppm, 2H, J = 11.7 Hz), 4.36 (ABq, Δδ = 0.19 ppm, 2H, J = 11.7 Hz), 4.41 (ABq, Δδ = 0.11 ppm, 2H, J = 11.4 Hz), 7.21 (m, 25H); ^{13}C NMR (C_6D_6) δ 34.47, 59.23, 71.23, 72.11, 73.25, 73.82, 73.88, 74.08, 75.10, 76.37, 77.92, 79.75, 80.08, 127.79, 128.06, 128.26, 128.39, 128.71, 128.93, 139.36, 139.48, 139.58, 139.66.

Chapter III

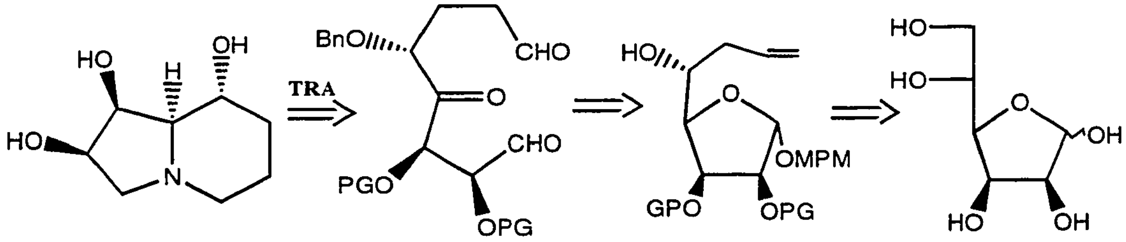
Syntheses of Analogues of Castanospermine

III.1 Synthesis of Swainsonine

Retrosynthesis

Like castanospermine **(I-1)**, the indolizidine, swainsonine **(I-2)**, has shown wide-ranging biological effects and has attracted considerable synthetic interest[7]. Following our TRA strategy swainsonine **(I-2)** may be related to a tricarbonyl precursor **(III-1)**. Compound **(III-1)** could be synthesized from the C5 allylated pyranoside **(III-2)** which may be derived from D-mannose **(III-3)**.

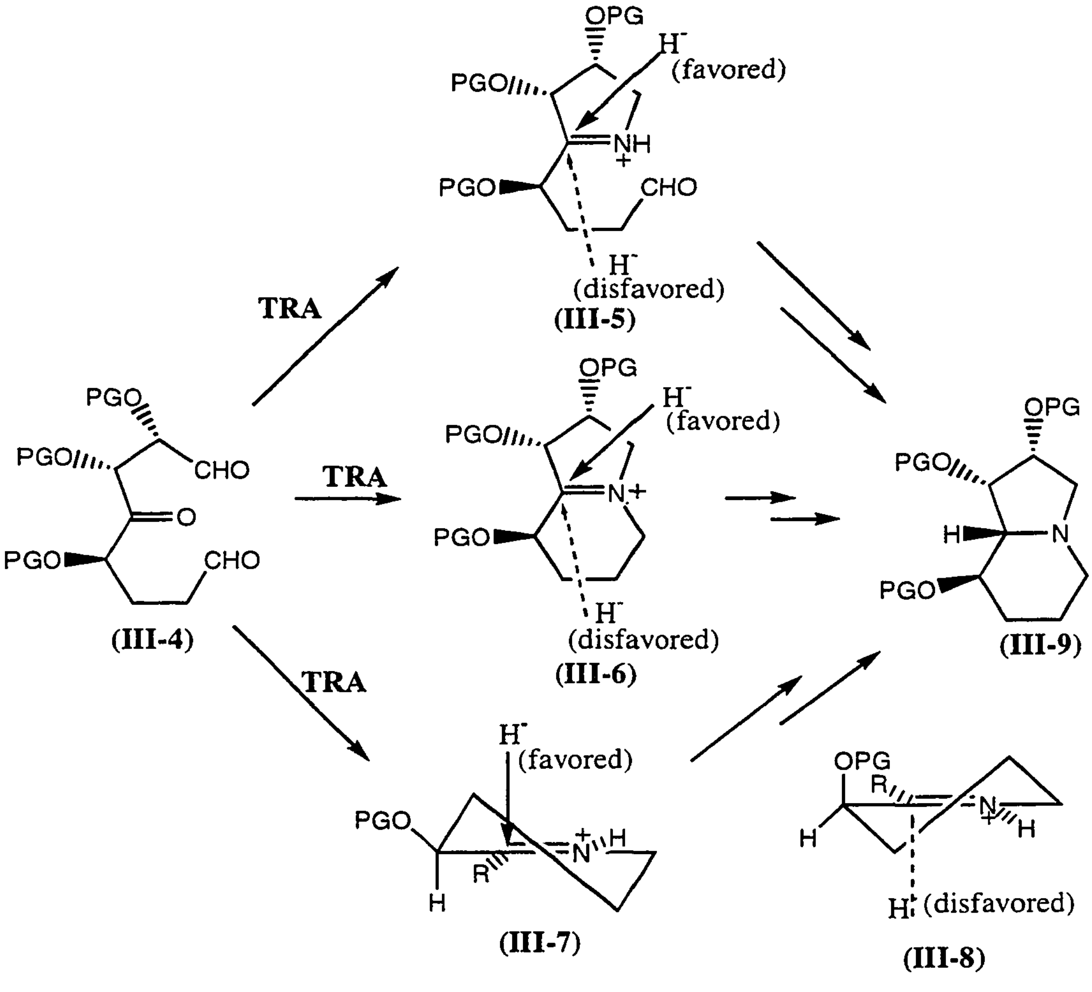
Scheme III-1.



Swainsonine (I-2) **(III-1)** **(III-2)** **D-Mannose (III-3)**

As for castanospermine, all three pathways are predicted to give the desired stereochemical result. Introduction of the C8a amine on the five membered ring iminium ion **(III-5)** is expected to proceed with reduction anti to the α-substitutent on the five membered ring. Also the reduction of the six membered iminium ion **(III-7)** from the top face is expected to be favored over bottom face attack on **(III-8)**. Similarly, reduction of the bicyclic iminium ion **(III-6)** should give product **(III-9)**. It should be noted that the favored direction of hydride attack is opposite to that obtained for castanospermine. With these considerations in mind the synthesis of swainsonine **(I-2)** was undertaken.

Scheme III-2



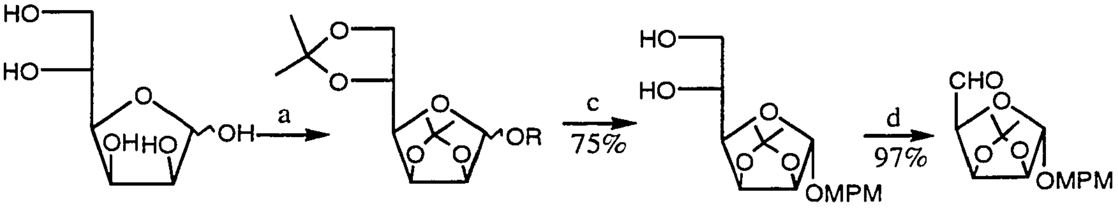
stable transition state

unstable transition state

Synthesis

The p-methoxybenzyl furanoside **(III-13)** was prepared from 2,3,5,6-di-O-isopropylidene–D-mannofuranose **(III-3)** via application of the procedure which was used for the methyl furanoside derivative[46]. Alkylation of **(III-10)** with p-methoxybenzyl chloride and sodium hydride, followed by selective hydrolysis of the 5,6-O-isopropylidene, and periodate cleavage of the resulting diol provided **(III-13)** in 73% overall yield.

Scheme III-3.



(III-3)

b **(III-10) R = H**

(III-11) R = MPM

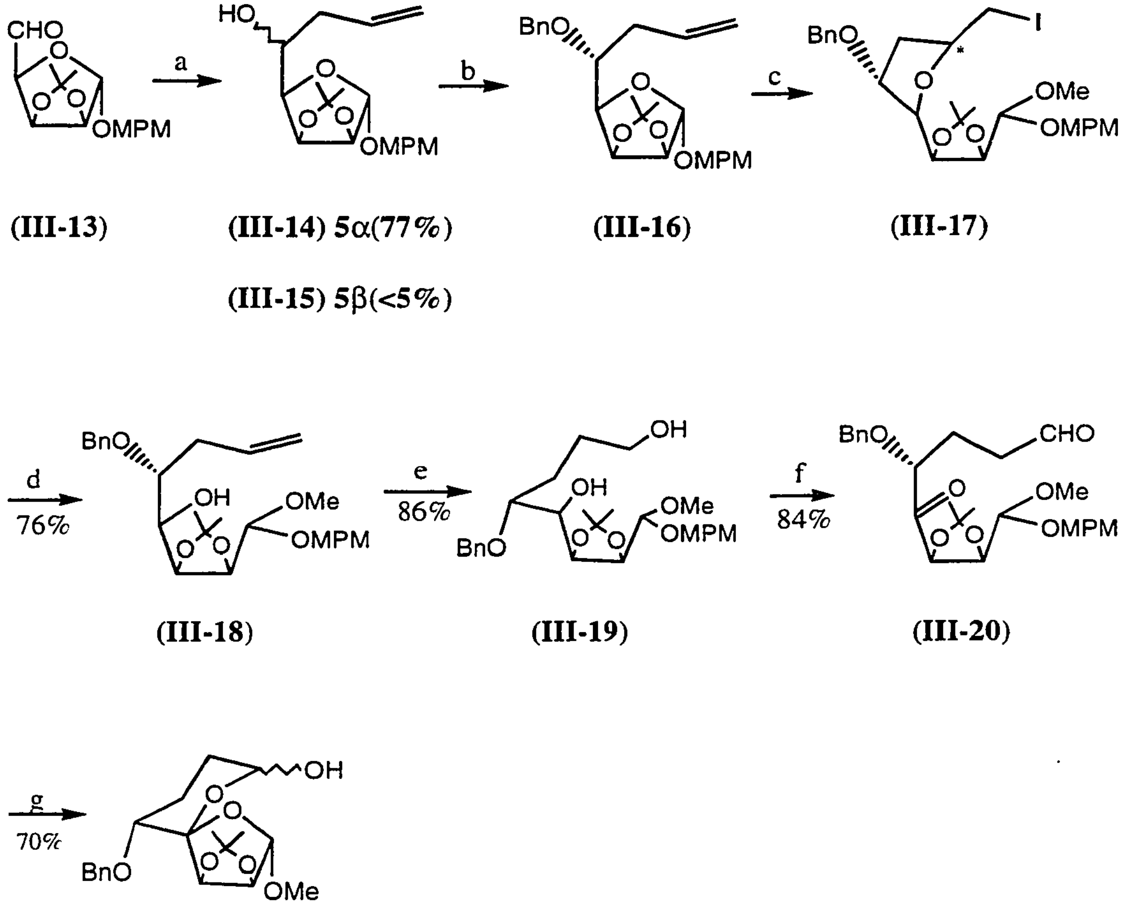
(III-12)

(III-13)

Key: (a) acetone, H_2SO_4, $CuSO_4$; (b) p-$ClCH_2C_6H_4OCH_3$, NaH, n-Bu_4NI, DMF; (c). Concentrate HCl, MeOH; (d) $NaIO_4$ (aq), MeOH;

Allylation of **(III-13)** under the conditions developed by Danishefsky (BF_3-Et_2O, allyltirmethylsilane, CH_2Cl_2, –78 °C) led almost exclusively to alcohol **(III-14)** in 77% yield with less than 5% diastereomer **(III-15)**[47]. Benzylation of the major product, followed by iodoetherification (IDCP, MeOH, CH_2Cl_2) of the benzyl ether **(III-16),** gave a mixture of iodo-THF's **(III-17).** Treatment **(III-17)** with zinc provided a single product **(III-18)** in 76% overall yield from **(III-14).** Hydroboration of **(III-18)** afforded diol **(III-19)** in 86% yield. Swern's oxidation of **(III-19)** led to the dicarbonyl product **(III-20).** DDQ mediated cleavage of the p-methoxybenzyl acetal provided a compound for which the structure **(III-21)** is suggested by the NMR data. The ^1H NMR shows signals at 3.50 ppm, 4.97 ppm and 4.66 ppm corresponding to the OMe and acetal hydrogens. No signals for carbonyl carbons were observed in the ^{13}C NMR, but resonances at 105.98 ppm, 104.20 and 92.22 ppm, matching the three acetal carbons were present.

Scheme III-4.

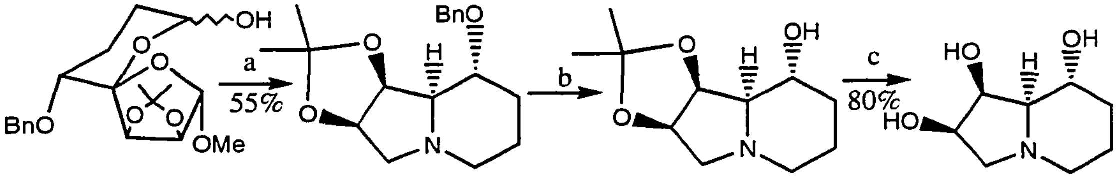


(III-21)

Key: (a) BF_3-Et_2O (1.5eq), Allyltirmethylsilane (1.2eq), CH_2Cl_2; (b) BnBr, NaH, n-Bu_4NI, DMF; (c) IDCP, MeOH (5eq), CH_2Cl_2; (d) Zn, 95% EtOH, reflux; (e) 9-BBN, THF, then H_2O_2 (30%), NaOH (3N); (f) Swern oxidation; (g) DDQ, CH_2Cl_2—H_2O (10:1);

The tricarbonyl precursor **(III-21)** was treated under the standard TRA conditions to give **(III-22)** in 55% yield. Debenzylation of **(III-22)** with Pd/C, followed by hydrolysis with 6M HCl gave swainsonine (**2**) in 80% yield. The ^{1}H and ^{13}C NMR of synthetic swainsonine were identical with natural product[48]. The overall yield from D-mannose (**III-3**) was 8.7% over 14 steps.

Scheme III-5.

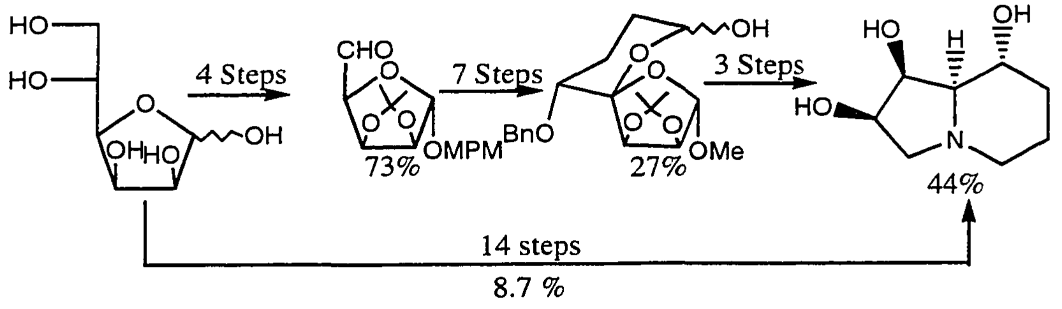


(III-21) **(III-22)** **(III-23)** **(I-2)**

Key: (a) 1.3(eq) NH_4HCO_2, 30 (eq) $NaCNBH_3$, MeOH; (b) Pd/C, HCOOH, H_2, MeOH; (c) HCl (6N), THF;

Synthesis of Swainsonine (I-2)

Scheme III-6.



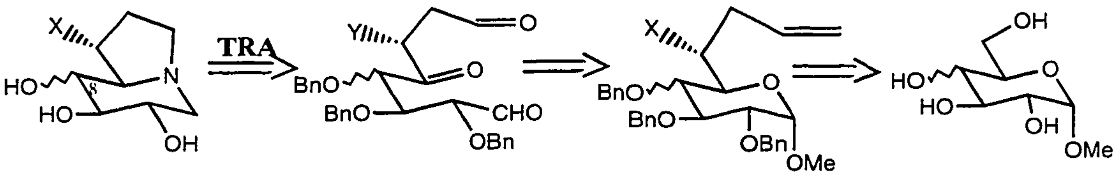
III.2 Synthesis of Unnatural Analogues

In order to test the scope of the methodology, as well as to get a clearer mechanistic picture of the TRA, the synthesis of 1-epi-, 1-deoxy- and 1,8-diepi-castanospermine **(I-3)**, **(I-4)** and **(I-5)**, was attempted. These analogues are also of interest in connection with structure – activity studies.

Retrosynthesis

The required tricarbonyl precursors **(III-24)**, **(III-25)** and **(III-27)** could be prepared from methyl α-D- gluco- or galacto- pyranoside (i.e. **(I-39)** or **(III-29)**).

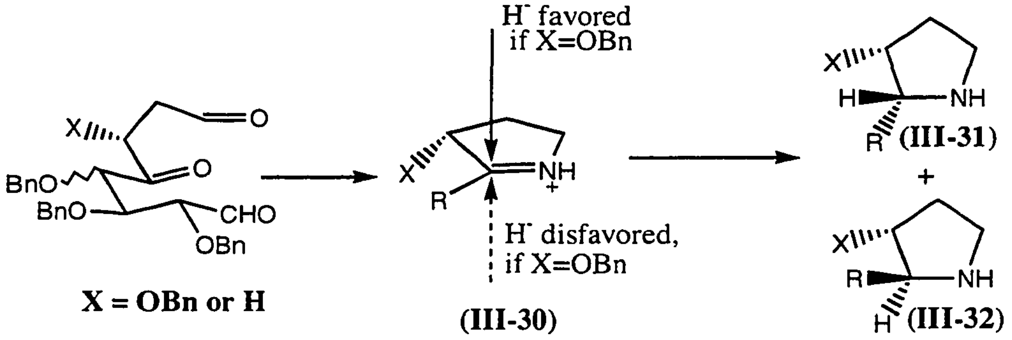
Scheme III-7.



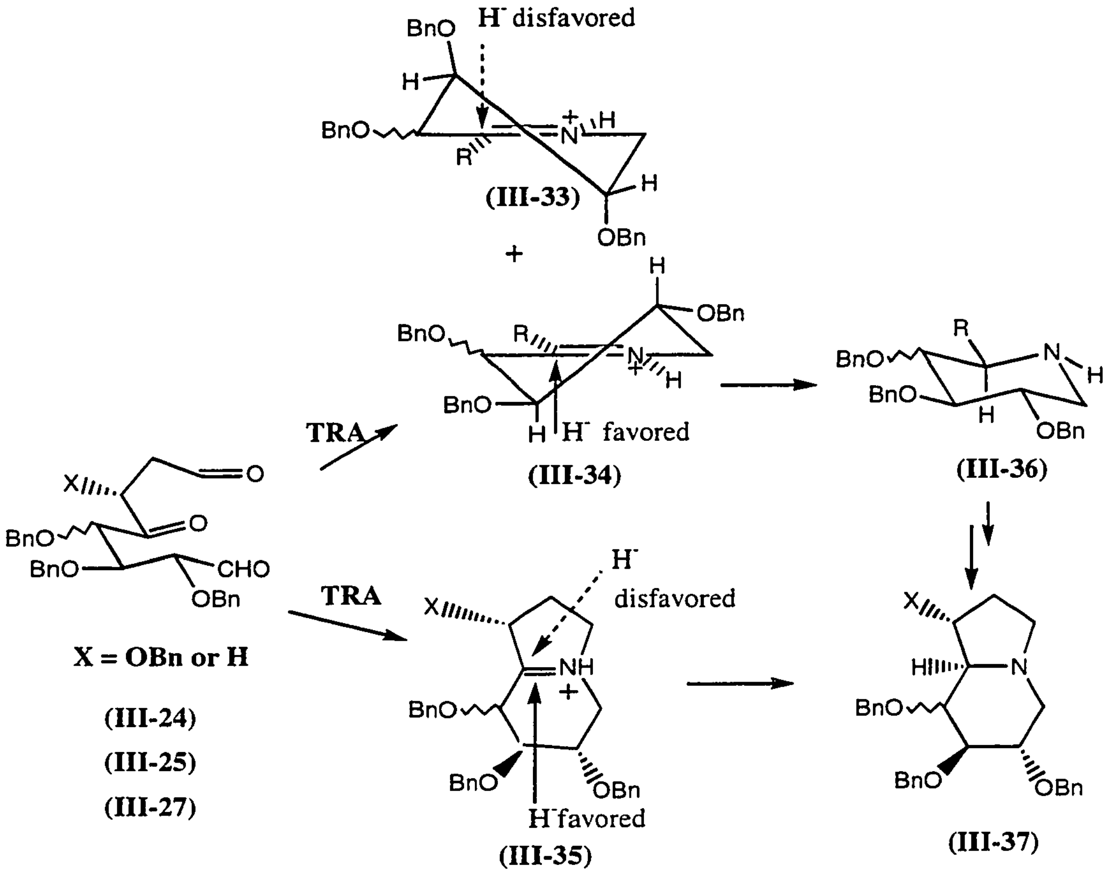
(I-3) X = OH, 8α-OH	**(III-24) Y =OBn**	**(II-6)**	**(I-37) 4α**
(I-4) X = H, 8α-OH	**(III-25) Y = H**	**(III-26)**	**(I-37) 4α**
(I-5) X = OH, 8β-OH	**(III-27) Y =OBn**	**(III-28)**	**(III-29) 4β**

As mention earlier reduction of five membered ring iminium ions of type **(III-30)** with X = OBn is expected to provide **(III-31)** as the major product. By comparison, reduction of deoxy derivative (X = H) is not expected to be stereoselective. Therefore, if reduction of the five membered ring iminium ions is a major pathway in the TRA, the reactions of the tricarbonyl precursors **(III-24)**, **(III-25)** and **(III-27)**), would be expected to give at best a mixture of 8a epimers. However, if the major pathway involved a six membered ring iminium ion, or 5, 6 fused iminium ion, a favored product from α face reduction of the iminium ion **(III-34)** or **(III-35)** would be expected. With these considerations in mind the cyclizations of **(III-24)**, **(III-25)** and **(III-27)** were examined.

Scheme III-8.



Scheme III-9.

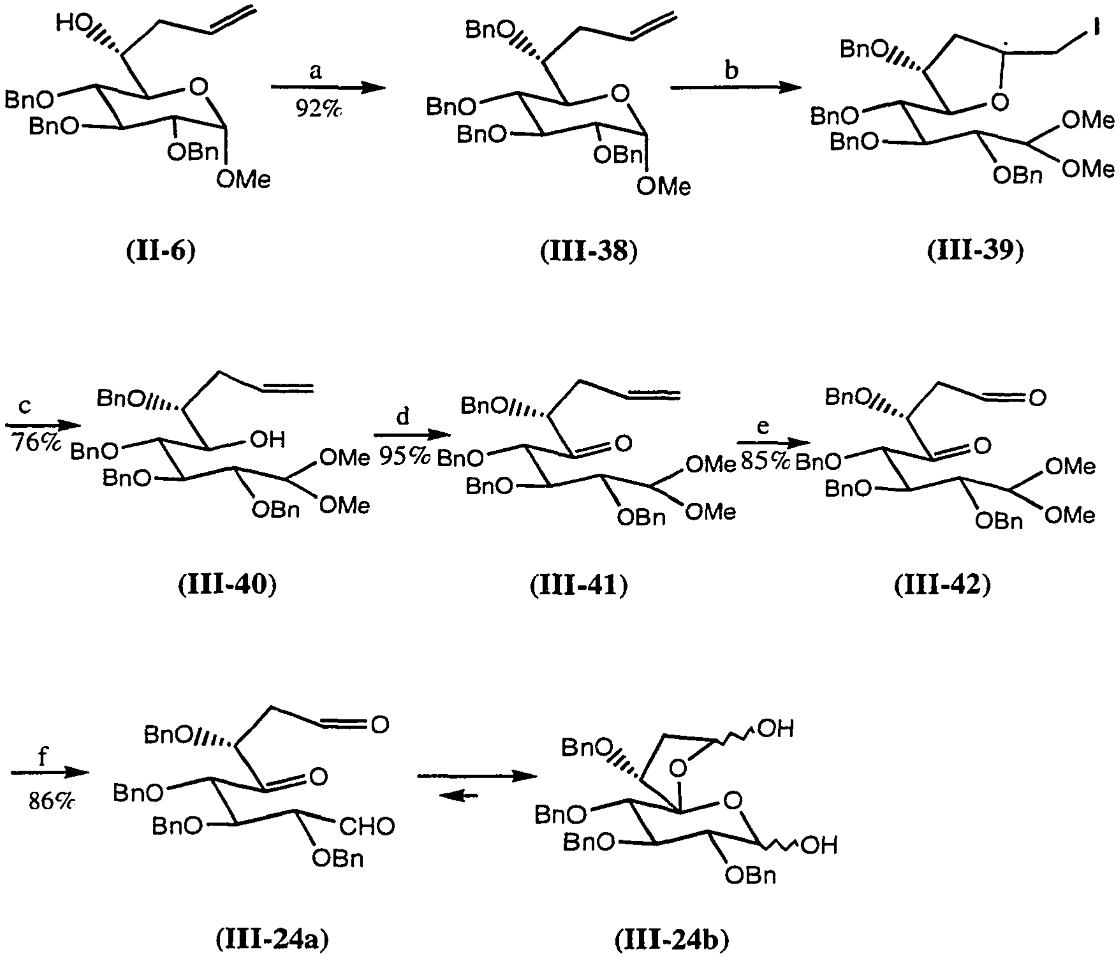


Synthesis of Tricarbonyl Precursors (III-24), (III-25) and (III-27)

1-Epi-castanospermine

The tricarbonyl precursor for 1-epi castanospermine **(III-24)** was prepared from the minor allylation product **(II-6)**, from the castanospermine synthesis (Scheme II-2). The conversion of **(II-6)** to **(III-24)** followed the corresponding procedures in the earlier work. (Scheme III-10)

Scheme III-10.

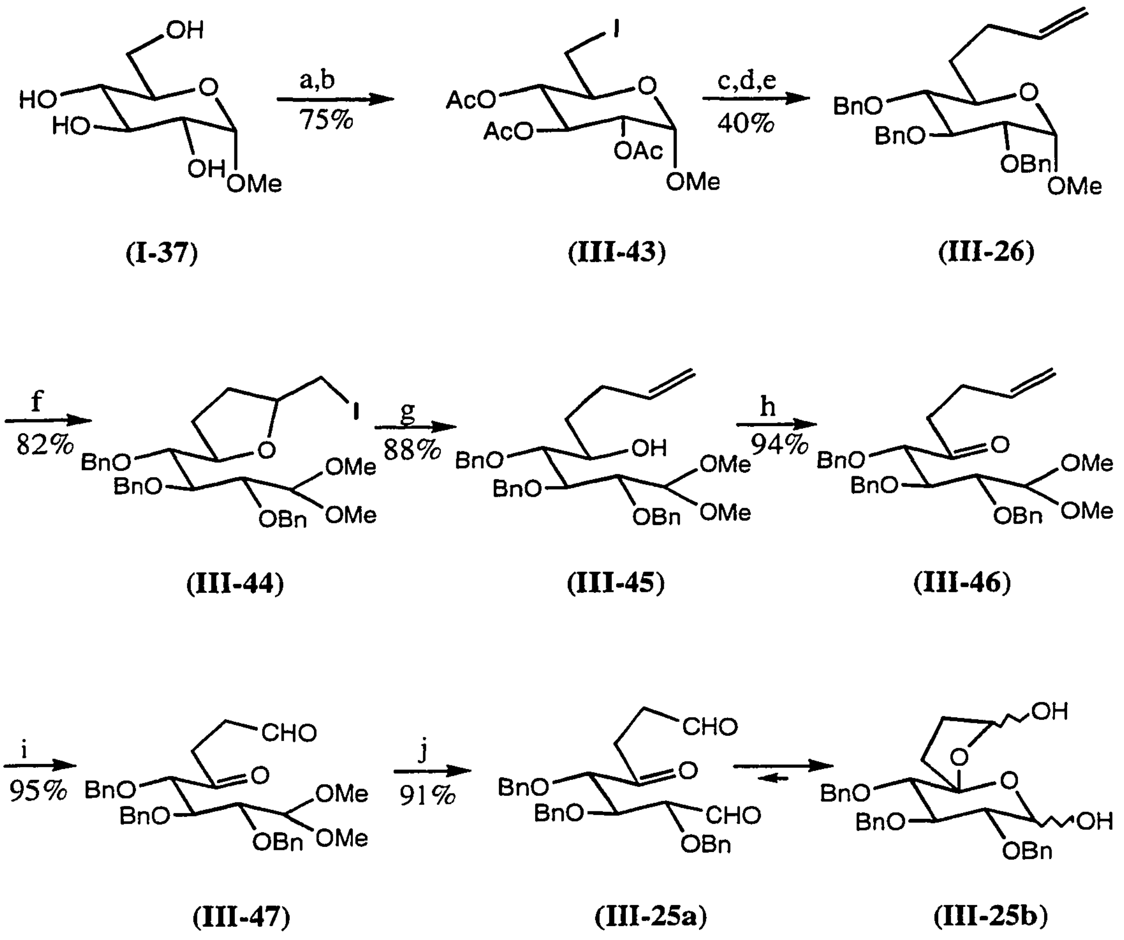


Key: (a) BnBr, NaH, n-Bu_4NI, DMF; (b) IDCP, CH_2Cl_2-MeOH; (c) Zn, 95% EtOH, reflux; (d) Swern oxidation; (e) O_3, CH_2Cl_2, -78°C then Ph_3P; (f) THF—9M HCl; (g) 1.3(eq) NH_4HCO_2, 30(eq) $NaCNBH_3$,

1-Deoxy-castanospermine.

The known D-glucose derivative **(III-26)** was prepared in five steps from methyl α-D-gluco pyranoside **(III-26)**. The key step was Keck allylation of the 6-iodo glucose derivative.[49] Compound **(III-26)** was transformed to the THF-dimethyl acetal **(III-44)** using IDCP and methanol as the nucleophile, with dichloromethane as solvent. The iodo THF **(III-44)** was converted to the tricarbonyl precursor **(III-25)** through the standard protocol of reductive elimination, alcohol oxidation, ozonolysis and acetal hydrolysis. As before ^{1}H-NMR spectrum of the product **(III-25)** showed acetal proton signals at δ 5.6 ppm. The absence of any aldehyde proton signal at δ 9.8 ppm suggested that the predominant tautomer was the acetal **(III-25b)**.

Scheme III-11.

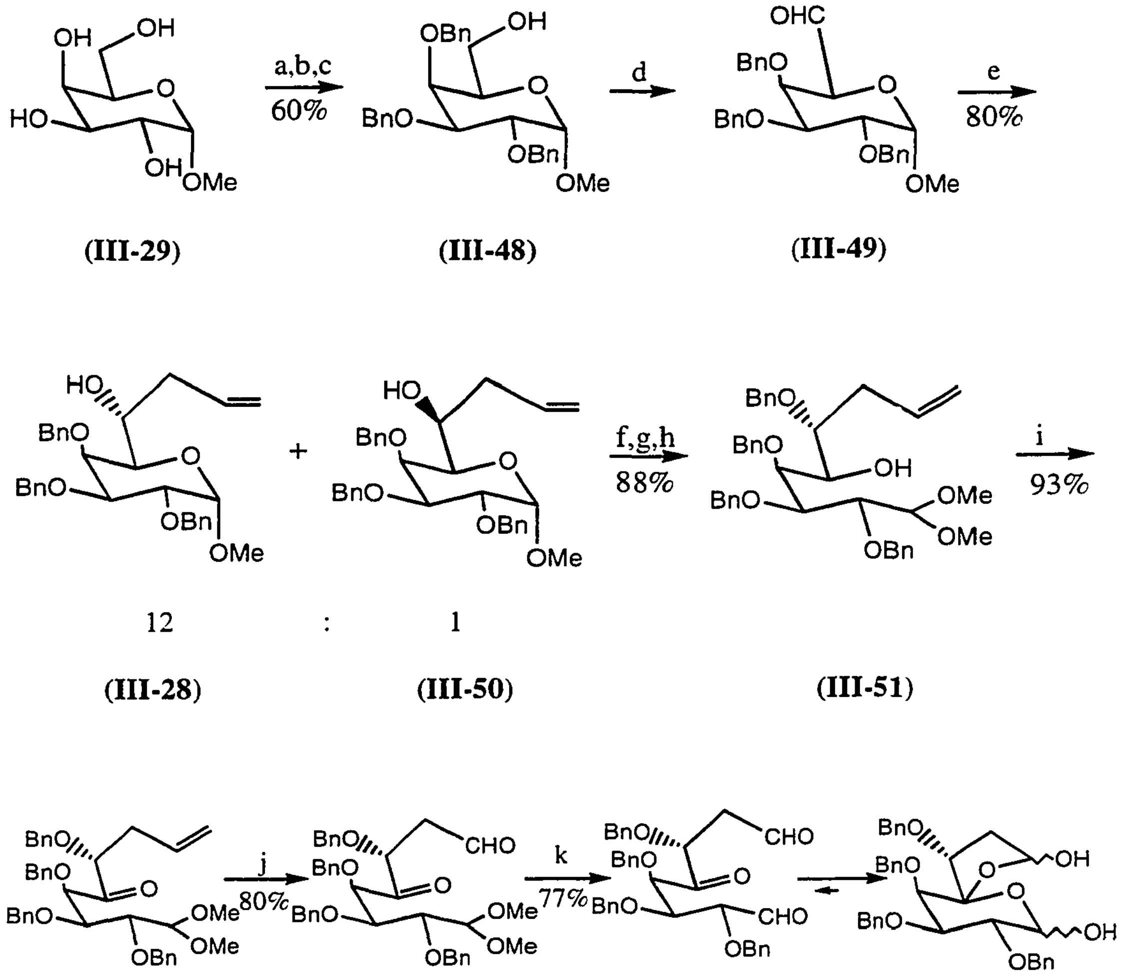


Key: a). I_2, Ph_3P, imidazole, toluene, CH_3CN; b). $(CH_3CO)_2$, EtOAc, dimethylaminopyridine; c). Allyl tributyl tin, AIBN, benzene; d). MeONa, MeOH; e). NaH, DMF, BnBr, Bu_4NI; f). IDCP, MeOH, CH_2Cl_2; g). Zn (active), HCl, EtOH (95%); h). $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; i). O_3, CH_2Cl_2; j). HCl (9N), THF, H_2O;

1,8-Diepi-castanospermine

A similar procedure to that used for the castanospermine precursor was used. The known D-galactose derivative **(III-49)**[50] was prepared in four steps from methyl α-D-galactopyranoside **(III-29)**. Allylation using tin powder and allyl bromide in CH_3CN-H_2O (10:1) as before, however gave the 6R-epimer **(III-28)** as the major product (80 % yield of **(III-50)** and **(III-28)**, 1:12). The stereochemistry of these products was tentatively assigned by NMR comparison with related materials.[40] Conversion of **(III-50)** to the carbonyl precursor was carried out as before. The product **(III-27)** did not show any aldehyde and ketone signals in the ^1H-NMR and ^{13}C-NMR. The NMR data was consistent with the acetal structure **(III-27b)**. This behavior is similar to the previously prepared keto-dialdehydes.

Scheme III-12.



(III-29) (III-48) (III-49)

(III-28) (III-50) (III-51)

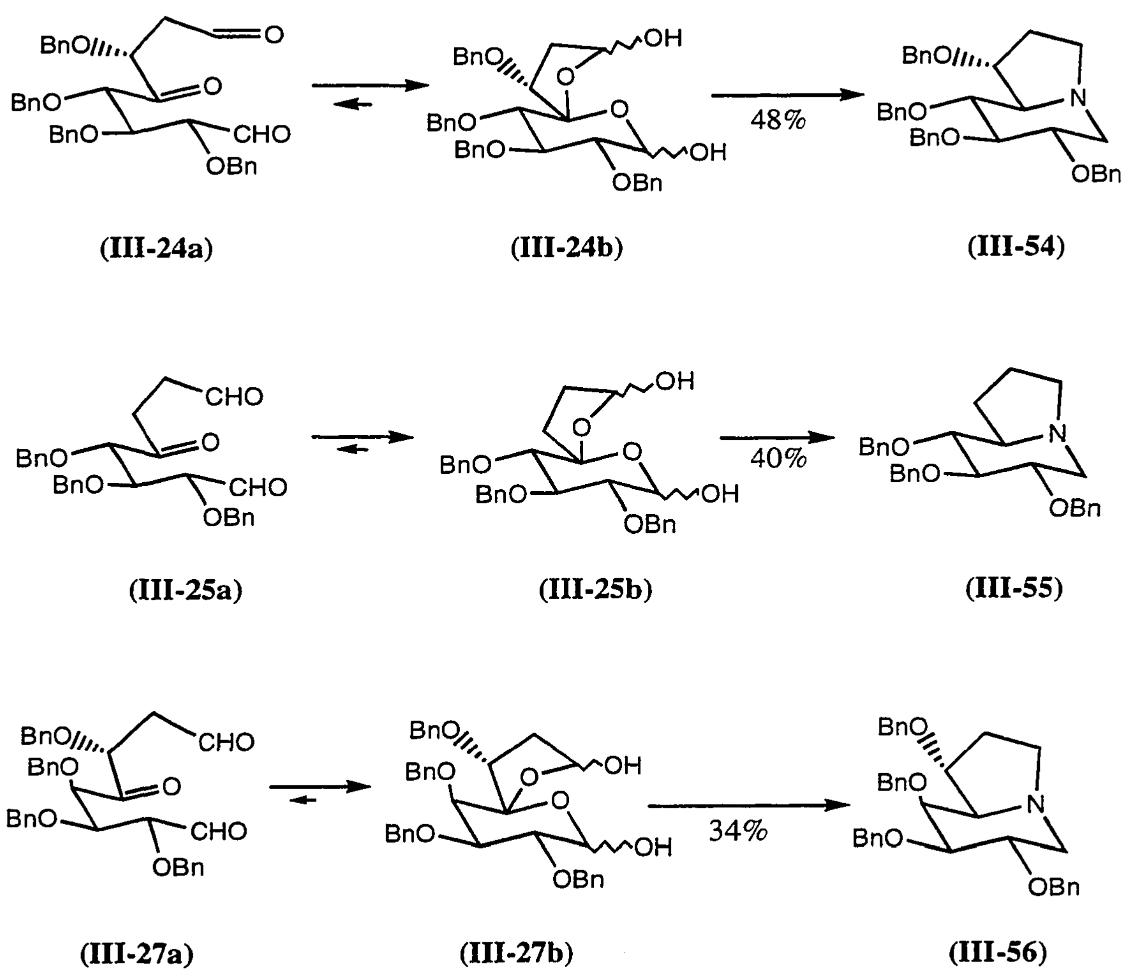
(III-52) (III-53) (III-27a) (III-27b)

Key: (a) TEA, Ph_3CCl, DMAP, DMF; (b) BnBr, NaH, Bu_4NI, THF; (c) HOAc, H_2O; (d) Swern's oxidation; (e) Sn powder, allyl bromide, CH_3CN-H_2O(10:1); (f) BnBr, NaH, n-Bu_4NI, DMF; (g) IDCP, MeOH (5eq), CH_2Cl_2; (h) Zn, 95% EtOH, reflux; (I) Swern's oxidation; (j) O_3, CH_2Cl_2, -78 °C then Ph_3P; (k) THF, 9M HCl;

Triple Reductive Aminations

Application of the standard TRA conditions (dry methanol, rt, 1.5 eq HCO_2NH_4, 30 eq $NaCNBH_3$, 48 h) to tricarbonyl derivatives **(III-24)**, **(III-25)** and **(III-27)** provided the indolizidine products **(III-54)**, **(III-55)** and **(III-56)** in 48, 40 and 34 % yield respectively.

Scheme III-13.



In all cases only a single C8a epimer was detected. The structures of the products were assigned from 1D and 2D ^{1}H NMR and ^{13}C NMR analysis. That the configuration at C8a was identical to that in castanospermine suggests that the initial formation of the pyrrolidine ring (i.e. Scheme III-8) is not a major reaction pathway. Thus it appears that the stereochemistry of the piperidine ring, either by way of the mono or the bicyclic iminium ions (i.e. Scheme III-9) controls the stereoselectivity of the TRA.

III.3 Summary

Table III-1.

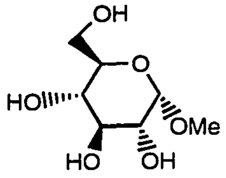
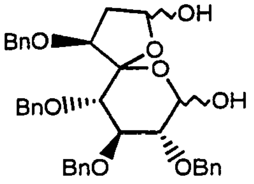
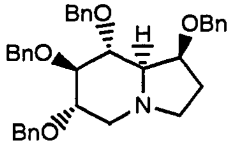
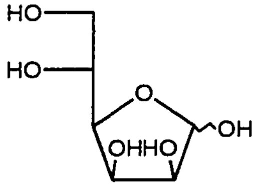
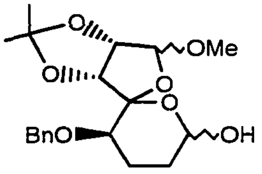
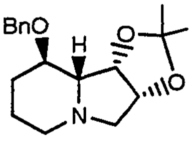
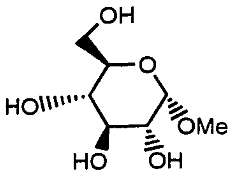
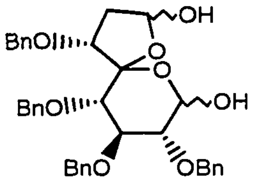
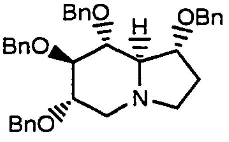
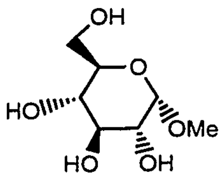
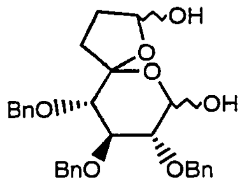
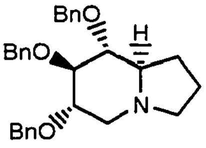
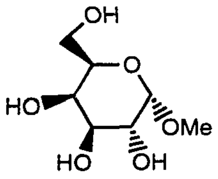
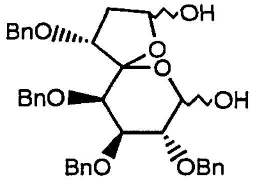
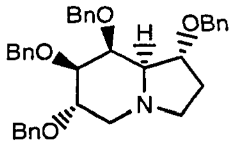
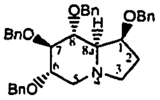
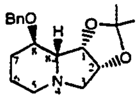
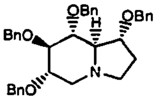
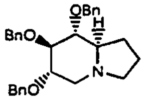
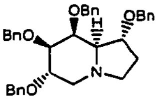
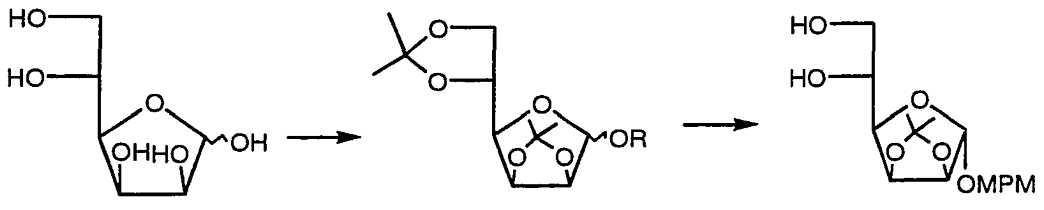
Starting Material	Tricarbonyl precursor	Product of TRA (%)
		 **(II-11)** 53%
		 **(III-22)** 55%
		 **(III-54)** 48%
		 **(III-55)** 40%
		 **(III-56)** 34%

Table III-2. ^1H NMR (ppm) of Polyhydroxyindolizidines

	 (II-11)	 (III-22)	 (III-54)	 (III-55)	 (III-56)
H1	3.93	4.52	3.84	1.23	4.20
				1.94	
H2	1.73	4.18	1.70	1.23	1.57
	1.73		1.88	1.41	2.20
H3	1.73	1.63	2.33	1.94	1.99
	2.89	2.97	2.62	2.79	2.79
H5	1.91	1.37	2.10	1.94	1.99
	3.15	2.61	3.06	3.14	3.19
H6	3.80	1.09	3.75	3.81	4.20
		1.33			
H7	3.68	1.07	3.64	3.64	3.38
		1.97			
H8	4.18	3.72	3.46	3.37	4.02
H8a	2.00	1.48	2.42	1.94	2.20

III.4 Experimental

III.4.1 Synthesis of 4-Methoxybenzyl 2,3-O-Isopropylidene-α-D-mannofuranoside (III-12)



(III-3)

(III-10) R = H

(III-11) R = MPM

(III-12)

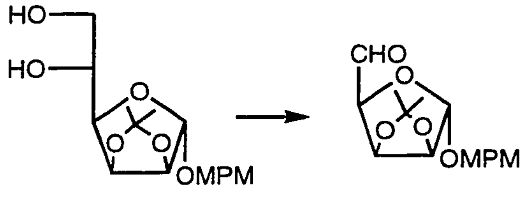
A mixture of D-mannose **(III-3)** (33.0 g, 183 mmol), anhydrous cupric sulfate (60.0 g), concentrated sulfuric acid (1.2 mL) and dry acetone (600 mL) was stirred at rt for 23 h. The pH of the reaction mixture was adjusted to 8 by addition of solid $NaHCO_3$. The suspension was filtered and filtrate was concentrated *in vacuo* to give crude **(III-10)**[46] (44.7 g). $R_f = 0.50$ (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 2.77 (br, 1H), 4.07 (m, 2H), 4.19 (dd, 1H, J = 3.6, 6.9 Hz), 4.41 (dd, 1H, J = 6.9, 11.1 Hz), 4.62 (d, 1H, J = 6.0 Hz), 4.81 (dd, 1H, J = 3.6, 8.7 Hz), 5.38 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 24.79, 25.49, 26.16, 27.15, 66.84, 73.48, 77.05, 79.88, 80.61, 85.71, 101.52, 112.84.

A portion of the crude material from previous step (10.0 g) was subjected to the general benzylation procedure, using 4-methoxybenzyl chloride instead of benzyl bromide. The crude 4-methoxybenzyl furanoside **(III-11)** (14.0 g) was obtained. R_f = 0.30 (EtOAc : P.E = 10 : 90); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.39 (s, 3H), 1.46 (s, 6H), 3.78 (s, 3H), 4.00 (m, 2H), 4.12 (dd, 1H, J = 8.7, 6.6 Hz), 4.43 (m, 1H), 4.50 (ABq, $\Delta\delta$ =

0.17 ppm, 2H, J = 11.7 Hz), 4.63 (d, 1H, J = 6.0 Hz), 4.78 (dd, 1H, J = 3.6, 6.0 Hz), 5.05 (s, 1H), 6.88 (d, 2H, J = 8.7 Hz), 7.25 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 24.56, 25.30, 25.93, 26.93, 55.26, 66.99, 68.76, 73.20, 79.64, 80.45, 85.18, 105.36, 109.21, 112.56, 113.83, 113.95, 129.39, 129.75, 159.45; Anal calcd for **(III-11)** $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. found: C, 63.55; H, 7.61.

Water was added to a mixture of concentrated HCl (2.0 mL), methanol (160 mL) and crude **(III-11)** until the solution became turbid. The reaction mixture was stirred for 3 h, at which time the pH was adjusted to neutral by adding concentrated aqueous ammonia. Most of methanol was removed *in vacuo*, and the aqueous residue extracted with ether (3 x). The organic extract was dried (Na_2SO_4), filtered and evaporated *in vacuo*. The crude residue was purified by flash chromatography to yield **(III-12)** (10.5 g, 75 %, after three steps). R_f = 0.30 (EtOAc : P.E = 50 : 50); ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.47 (s, 3H), 2.42 (br, 2H), 3.70 (dd, 1H, J = 5.4, 11.4 Hz), 3.80 (s, 3H), 3.85 (m, 1H), 4.00 (m, 2H), 4.49 (ABq, Δδ = 0.15 ppm, 2H, J = 11.4 Hz), 4.63 (d, 1H, J = 6.0 Hz), 4.84 (dd, 1H, J = 3.6, 6.0 Hz), 5.09 (s, 1H), 6.87 (d, 2H, 8.7 Hz), 7.24 (d, 2H, 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 24.80, 26.10, 55.45, 64.66, 68.94, 70.50, 79.46, 80.30, 85.03, 105.31, 112.81, 114.07, 129.52, 129.90, 159.56.

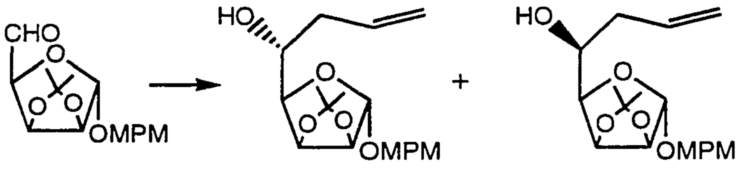
III.4.2 Synthesis of 2,3-O-Isopropylidene Aldehyde (III-13)



(III-12) **(III-13)**

A solution of $NaIO_4$ (3.7 g, 17.5 mmol) in a minimum amount of water was added to a solution of diol **(III-12)** (4.95 g, 14.5 mmol) in methanol (100 mL). The reaction mixture was stirred at rt for one hour, at which time most of methanol was evaporated under reduced pressure. Saturated NaS_2O_3 solution (50 mL) was poured into the residual solution and the aqueous mixture extracted with ether (3 x). The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the residue gave **(III-13)** (4.35 g, 97 %). $R_f = 0.50$ (EtOAc : P.E = 50 : 50); ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.42 (s, 3H), 3.79 (s, 3H), 4.44 (m, 1H), 4.63 (m, 3H), 4.90 (m, 1H), 5.10 (m, 1H), 6.88 (m, 2H), 7.26 (m, 2H), 9.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.61, 25.90, 55.32, 68.96, 80.99, 84.45, 105.70, 113.98, 128.92, 129.81, 129.87, 159.58, 197.81.

III.4.3 Synthesis of 2,3-O-Isopropylidene Alcohol (III-14)



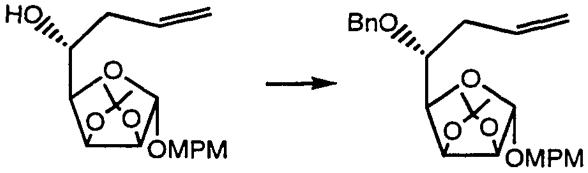
(III-13) **(III-14)** **(III-15)**

Boron trifluoride etherate (4.9 mL, 39.4 mmol) was added to a solution of aldehyde **(III-13)** (8.1 g, 26.2 mmol) in dry CH_2Cl_2 (300 mL) at –78°C. The solution was stirred at –78°C for 20 min at which time allyltirmethylsilane (5.0 mL, 31.4 mmol) was added, and the reaction stirred for 2 h at –78°C. The solution was poured into the saturated aqueous $NaHCO_3$ (300mL) and the mixture extracted with ether (3 x 200 mL). The combined organic layer was washed with brine (200 mL), dried (Na_2SO_4), filtered and evaporated in vacuo. Flash chromatography afforded a major and minor products, **(III-14)** and **(III-15)** respectively.

For **(III-14)** (7.2 g, 76.7%). R_f = 0.50 (EtOAc : P.E = 20 : 80); $[\alpha]_D$ +66.9 (c = 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.50 (s, 3H), 2.36 (m, 1H), 2.59 (m, 1H), 3.83 (s, 3H), 3.88 (dd, 1H, J = 3.90, 3.75 Hz), 4.03 (m, 1H), 4.53 (ABq, Δδ = 0.13 ppm, J = 11.4 Hz, 2H), 4.65 (d, 1H, J = 6.0 Hz), 4.87 (dd, 1H, J = 6.0, 3.75 Hz) 5.12 (s, 1H), 5.20 (m, 2H), 5.98 (m, 1H), 6.91 (d, 2H), 7.27 (d, 2H); ^{13}C NMR ($CDCl_3$) δ 24.76, 26.09, 39.11, 55.40, 68.75, 69.43, 80.22, 81.54, 85.15, 105.15, 112.71, 114.06, 117.87, 129.58, 129.84, 134.58, 159.56; Anal calcd for **(III-14)** $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. found: C, 65.06; H, 7.48.

For **(III-15)** (0.3 g) less than 5%; R_f = 0.55 (EtOAc : P.E = 20:80); ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 1.46 (s, 3H), 2.43 (m, 2H), 3.13 (broad, 1H), 3.78 (s, 3H), 3.89 (dd, 1H, J = 5.1, 3.6 Hz), 4.10 (m, 1H), 4.51 (ABq, Δδ = 0.15 ppm, J = 11.4 Hz, 2H), 4.63 (d, 1H, J = 5.7 Hz), 4.73 (dd, 1H, J = 5.7, 3.6 Hz) 5.13 (s, 1H), 5.14 (m, 2H), 5.91 (m, 1H), 6.87 (d, 2H, J = 8.7 Hz), 7.27 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 24.46, 25.92, 37.87, 55.23, 68.67, 69.53, 80.46, 81.07, 85.52, 104.71, 112.62, 113.90, 117.50, 129.34, 129.78, 134.52, 159.40.

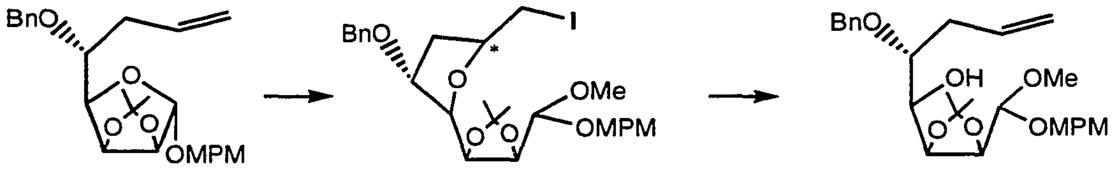
III.4.4 Synthesis of 5-O-Benzyl-2,3-O-Isopropylidene Alkene (III-16)



(III-14) **(III-16)**

The alcohol **(III-14)** (1.4 g, 4.3 mmol) was benzylated according to the general procedure (II.4.2), using NaH (0.52 g, 60% suspension in oil, 12.8 mmol), BnBr (1.02 mL, 8.6 mmol) and Bu_4NI (0.158 g, 0.43 mmol). Compound **(III-16)** (1.7 g, 96.6%) was obtained. R_f = 0.60 (EtOAc : P.E = 10 : 90); $[\alpha]_D$ +34.3 (c = 0.019 g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.45 (s, 3H), 2.39 (m, 1H), 2.61 (m, 1H), 3.79 (s, 3H), 3.90 (m, 2H), 4.47 (ABq, $\Delta\delta$ = 0.17 ppm, J = 11.1 Hz, 2H), 4.59 (d, 1H, J = 6.0 Hz), 4.65 (s, 2H), 4.81 (dd, 1H, J = 3.3, 6.0 Hz), 5.03 (s, 1H), 5.16 (m, 2H), 5.98 (m, 1H), 6.86 (d, 2H, J = 8.4 Hz), 7.23 (d, 2H, J = 8.4 Hz), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.16, 26.377, 36.43, 55.48, 68.61, 72.70, 76.00, 80.04, 80.60, 85.22, 105.23, 112.38, 114.09, 127.72, 128.19, 128.43, 129.66, 129.98, 134.76, 139.01; HRMS (FAB) calcd for $C_{26}H_{32}O_6$: 439.2120. found: M.W: 439.2119.

III.4.5 Synthesis of Hydroxy Alkene (III-18)

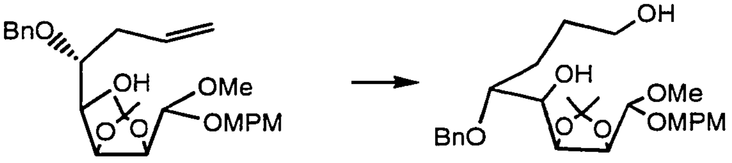


(III-16) **(III-17)** **(III-18)**

IDCP (14.9 g, 31.7 mmol) was added to a solution of alkene **(III-16)** (9.3 g, 21.1 mmol) in a mixture of CH_2Cl_2 (250 mL) and MeOH (3.16 mL, 105.5 mmol) under argon. The reaction mixture was stirred at rt for 1h, then poured into 10% aqueous $Na_2S_2O_3$, and extracted with ether (3 x 150 mL). The organic phase was washed with brine (150 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo,* to provided crude **(III-17).** A sample of this material was purified by flash chromatography for characterization purpose. R_f = 0.60 (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.46 (s, 1.5H), 1.49 (s, 1.5H), 1.79 (m, 0.5H), 2.01 (m, 0.5H), 2.22 (m, 0.5H), 2.31 (m, 0.5H), 3.23 (m, 2H), 3.65 (s, 3H), 3.74 (s, 3H), 4.17 (m, 2H), 4.31 (m, 3H), 4.47 (s, 2H), 4.63 (m, 1H), 4.76 (m, 1H), 5.11 (m, 1H), 6.80 (m, 2H), 7.29 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 24.59, 25.22, 26.82, 27.00, 37.25, 38.66, 52.96, 53.28, 55.30, 69.16, 69.52, 71.10, 71.54, 76.32, 76.72, 79.40, 80.01, 82.26, 82.64, 82.85, 83.10, 101.04, 101.39, 108.65, 109.01, 113.82, 113.96, 127.39, 127.66, 128.45, 130.19, 130.24, 138.27, 157.43, 159.49.

The resultant syrup **(III-17)** was dissolved in 95% ethanol (150 mL) and stirred with freshly activated powdered zinc (12 g) at reflux for 1 h. The suspension was then diluted with ether and filtered through a short column of florisil. Concentration of the filtrate *in vacuo* followed by flash chromatography of the residual, dark brown oil afforded hydroxy alkene **(III-18)** (7.8 g, 78.2 %). $R_f = 0.50$ (EtOAc : P.E = 20 : 80); $[\alpha]_D$ – 41.3 (c = 2.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.49 (s, 3H), 2.33 (d, 1H, J = 11.7Hz, from OH), 2.34 (m, 1H), 2.56 (m, 1H), 3.42 (s, 3H), 3.70 (s, 3H), 3.77 (t, 1H, J = 9.0 Hz), 4.25 (t, 1H, J = 7.2 Hz), 4.47 (d, 1H, J = 7.2 Hz), 4.51 (t, 2H, J = 11.4 Hz), 4.60 (t, 2H, J = 11.1 Hz), 4.94 (d, 1H, J = 7.2 Hz), 5.08 (m, 2H), 5.88 (m, 1H), 6.79 (d, 2H, J = 8.7 Hz), 7.22 (d, 2H, J = 8.7 Hz), 7.27 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.46, 26.78, 34.87, 53.39, 55.21, 69.26, 71.96, 74.81, 75.99, 79.22, 101.08, 108.26, 113.88, 117.28, 127.54, 127.72, 128.30, 129.83 (several lines), 134.70, 138.55, 159.42; Anal calcd for **(III-18)** $C_{27}H_{36}O_7$: C, 68.62; H, 7.68. found: C, 68.14; H, 7.87.

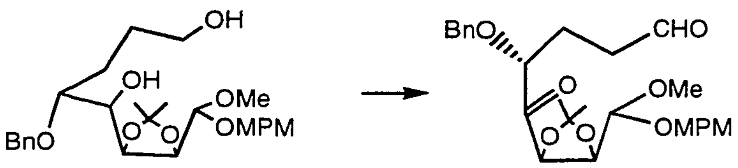
III.4.6 Synthesis of Diol (III-19)



(III-18) **(III-19)**

0.5 M 9-BBN (73.8 mL of a solution in THF, 36.9 mmol) was added at 0 °C, to a solution of **(III-18)** (5.8g, 12.3mmol) in dry THF (250mL). After 1 h, the reaction was warmed to rt and stirred 18 h at this temperature. The reaction was then cooled to 0 °C, and a mixture of 30% H_2O_2 (55 mL) and 30% NaOH (55 mL) was added. The solution was extracted with ether (3 x 200 mL). The combined organic layer was washed with brine (200 mL), dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the crude compound gave diol **(III-19)** (5.2g, 86.4%). $R_f = 0.30$ (EtOAc : P.E = 50 : 50); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.50 (s, 3H), 1.60 (m, 3H), 1.80 (m, 1H), 2.69 (d, 1H, J = 8.7 Hz), 2.90 (br, 1H), 3.42 (s, 3H), 3.55 (m, 2H), 3.68 (s, 3H), 3.78 (t, 1H, J = 8.1 Hz), 4.27 (t, 1H, J = 7.5 Hz), 4.48 (ABq, 2H, $\Delta\delta = 0.08$ ppm, J = 11.7 Hz), 4.53 (ABq, 2H, $\Delta\delta = 0.22$ ppm, J = 10.8 Hz), 4.97 (d, 1H, J = 7.2 Hz), 6.80 (d, 2H, J = 8.7 Hz), 7.26 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 24.32, 26.43, 26.53, 27.26, 53.17, 54.99, 62.51, 69.09, 71.73, 74.86, 75.82, 79.19, 100.93, 113.75, 127.35, 127.51, 128.12, 129.39, 129.61, 138.37.

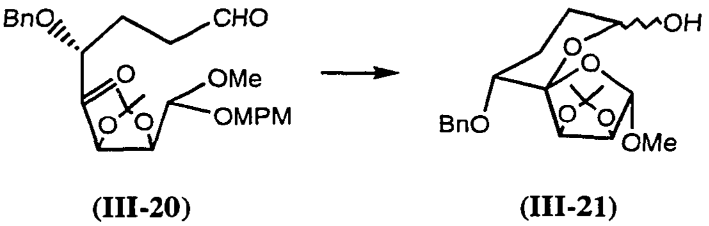
III.4.7 Synthesis of Keto Aldehyde (III-20)



(III-19) **(III-20)**

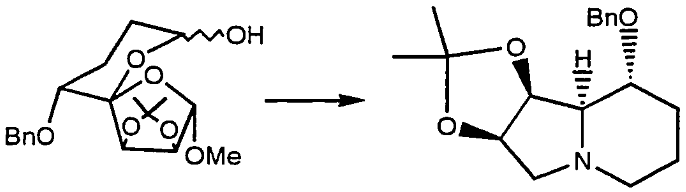
The standard Swern's oxidation procedure was applied to diol **(III-19)** (2.3 g, 4.7 mmol), using DMSO (2.0 mL, 28.2 mmol), oxalyl chloride (2.1 mL, 23.5 mmol) and Et_3N (6.8 mL, 47 mmol). Keto-aldehyde **(III-20)** (1.9g, 84%) was obtained as a brown oil. $R_f = 0.75$ (EtOAc : P.E = 50:50); $[\alpha]_D$ −17.2 (c = 7.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 3H), 1.54 (s, 3H), 1.76 (m, 1H), 1.96 (m, 1H), 2.32 (m, 2H), 3.37 (s, 3H), 3.71 (s, 3H), 3.92 (dd, 1H, J = 8.1, 3.9 Hz), 4.28 (dd, 2H, J = 11.4, 14.1 Hz), 4.42 (t, 1H, J = 6.6 Hz), 4.52 (t, 2H, J = 13.8 Hz), 4.63 (d, 1H, J = 6.0 Hz), 4.79 (d, 1H, J = 6.6 Hz), 6.78 (d, 2H, J = 8.4 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.24 - 7.26 (m, 7H), 8.50; ^{13}C NMR ($CDCl_3$) δ 23.12, 25.37, 26.98, 39.65, 54.23, 55.19, 68.65, 72.53, 76.68, 78.13, 81.87, 100.47, 110.63, 113.75, 127.93 -129.69 (several lines), 137.43, 159.34, 201.35, 205.08; HRMS (FAB) calcd for $C_{27}H_{34}O_8$: 485.2175. found: 485.2176.

III.4.8 Synthesis of Tricarbonyl Precursor (III-21)



DDQ (0.39 g, 1.73 mmol) was added at 0°C, to the solution of **(III-20)** (0.56 g, 1.15 mmol) in CH_2Cl_2 (20 mL) and H_2O (0.9 mL). After 20 min, the reaction mixture warmed to rt, additional water (1.0 mL) was added, stirred, continued for 1.5 h. The reaction was quenched by adding saturated $NaHCO_3$ (20 mL), and the mixture extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phase was washed with brine (25mL), dried ($NaSO_4$), filtered and evaporated *in vacuo*. Flash chromatography of the residue gave recovered starting material (0.13g, 0.27mmol) and compound **(III-21)** (0.21g, 70.4%). R_f = 0.3 (EtOAc : P.E = 50 : 50); $[\alpha]_D$ −68.8 (c = 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.30 (m, 1H), 1.43 (s, 3H), 1.46 (m, 1H), 1.78 (broad, 2H), 3.50 (s, 3H), 3.54 (s, 1H), 3.75 (d, 1H, J = 10.8 Hz), 4.50 (m, 3H), 4.67 (m, 1H), 4.97 (d, 1H, J = 3.6 Hz), 7.21-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.72, 25.41, 26.13, 28.06, 58.52, 70.84, 71.94, 78.41, 83.03, 92.23, 104.20, 105.97, 113.06, 127.73, 128.24, 128.42, 138.40.

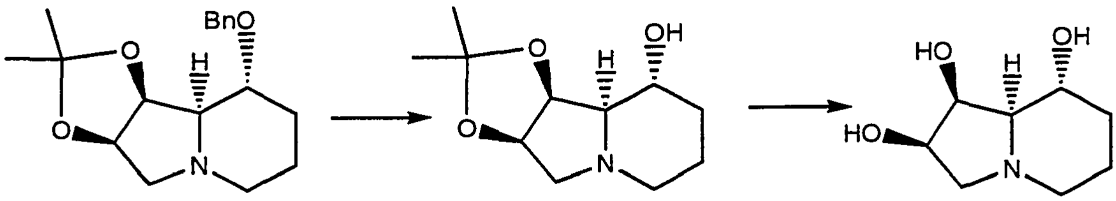
III.4.9 Synthesis of (1S, 2R, 8R, 8aR)-8-O-Benzyl 1,2-O-Isopropylidene Indolizidine (III-22)



(III-21) **(III-22)**

Ammonium formate (29 mg, 0.41mmol) and $NaCNBH_3$ (680 mg, 6.4 mmol) was added to a solution of **(III-21)** (120 mg, 0.32mmol) in anhydrous MeOH (15 mL). The reaction mixture was stirred for 24 h, at which time most of the solvent was removed in vacuo. The slurry was diluted with saturated aqueous Na_2CO_3, and the resulting suspension extracted with $CHCl_3$ (4 x 10 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the crude residue gave **(III-22)** (55mg, 55.4%). $R_f = 0.50$ (EtOAc : P.E = 50 : 50); $[\alpha]_D$ – 67.3 (c = 3.1, $CHCl_3$); ^1H NMR (C_6D_6) δ 1.07 (m, 1H), 1.09 (m, 1H), 1.21 (s, 3H), 1.33 (m, 1H), 1.37 (m, 1H), 1.48 (m, 1H), 1.51 (s, 3H), 1.64 (dd, 1H, J = 10.2, 4.5 Hz), 1.97 (m, 1H), 2.61 (m, 1H), 2.97 (d, 1H, J = 10.2 Hz), 3.72 (m, 1H), 4.18 (dd, 1H, J = 6.0, 4.8 Hz), 4.52 (dd, 1H, J = 6.0, 4.2 Hz), 4.61 (ABq, $\Delta\delta$ = 0.01 ppm, J = 10.8 Hz, 2H), 7.05-7.38 (m, 5H); ^{13}C NMR (C_6D_6) δ 24.73, 26.10, 27.03, 31.41, 52.07, 61.24, 71.81, 73.12, 74.89, 78.86, 80.52, 11.63, 127.78-128.72 (several lines), 140.65.

III.4.10 Synthesis of Swainsonine ((1R,2R,8R,8aR) 1,2,8 Trihydroxy Indolizidine) (I-2)



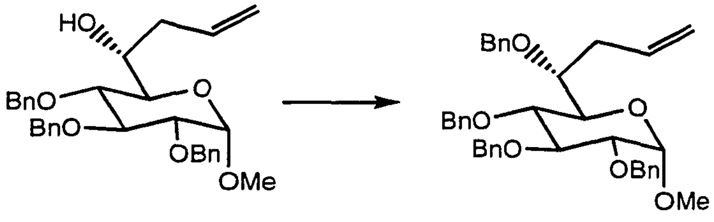
(III-22) **(III-23)** **(I-2)**

10% Pd/C (500 mg) was added to a solution of **(III-22)** (86 mg, 0.22 mmol) in MeOH (4 mL) under an argon atmosphere. HCOOH (1.0 mL) was added to the suspension, the mixture stirred for 2h, then filtered through a pad of celite. The filter cake was washed several times with methanol, then concentrated *in vacuo* to provided crude **(III-23)**. $R_f = 0.30$ (EtOAc : P.E = 50 : 50); ^{1}H NMR ($CHCl_3$) δ 1.31 (s, 3H), 1.42 (m, 2H), 1.53 (s, 3H), 1.81 (br, 2H), 2.10 (m, 1H), 2.38 (m, 2H), 2.61 (m, 1H), 3.30 (m, 1H), 3.45 (m, 1H), 4.06 (br, 1H), 4.73 (br, 1H), 4.81 (br, 1H): ^{13}C NMR ($CHCl_3$) δ 22.00, 24.11, 25.53, 31.80, 51.56, 59.27, 65.81, 72.38, 78.60, 97.57, 112.09.

The crude sample of **(III-23)** was stirred in a solution of 6N HCl (1 mL) and THF (3 mL) for 2 h, The volatile was then evaporated *in vacuo*, and the residual syrup was dissolved in ethanol and stirred with Amberlite IRA-(OH) ion exchange resin (500 mg) for 30 min. The mixture was filtered through celite and the filtrate concentrated *in vacuo* to give a semisolid residue **(I-2)** (39 mg, 80%). $R_f = 0.30$ (EtOAc : CH_3OH = 70 : 30);

$[\alpha]_D$ –85.7 (c = 0.3, CH_3OH) (lit[25] $[\alpha]_D$ –85.7 (c = 1.03, CH_3OH)); ^1H NMR (D_2O) δ 1.21 (m, 1H), 1.49 (m, 1H), 1.66 (broad, 1H), 1.86 (dd, 1H, J = 3.6, 9.0 Hz), 1.93 (dd, 1H, J=2.7, 14.3 Hz), 2.02 (m, 1H), 2.49 (dd, 1H, J = 13.2, 9.8 Hz), 2.83 (dd, 1H, J = 13.2, 2.1 Hz), 2.87 (broad, 1H), 3.76 (dt, 1H, J = 3.9, 10.2 Hz), 4.19 (dd, 1H, J = 3.9, 5.7 Hz), 4.30 (m, 1H); ^{13}C NMR (D_2O) δ 23.55, 32.86, 52.04, 61.26, 66.76, 69.37, 70.03, 73.28; identical with natural product.[48]

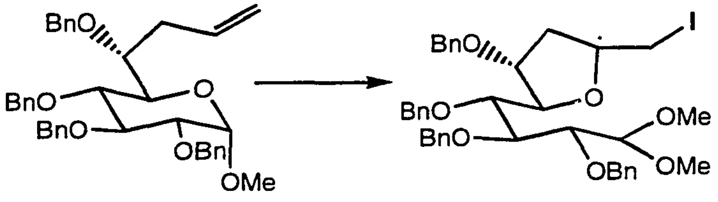
III.4.11 Synthesis of Pyranoside Alkene (III-34)



(II-5) **(III-38)**

The general procedure for the benzylation of alcohol was applied to **(II-5)** (1.25 g, 2.5 mmol), using NaH (0.30 g, 60% suspension in oil, 7.5 mmol), n-Bu_4NI (0.09 g, 0.25 mmol) and benzyl bromide (0.59 mL, 5.0 mmol). Flash chromatography of the crude product afforded recovered starting material (0.32 g) and pyranoside alkene **(III-38)** (1.09 g, 92% base on recovered **(II-5)**); R_f = 0.70 (EtOAc : PE = 20 : 80); ^1H NMR ($CDCl_3$) δ 2.15 (m, 1H), 2.39 (m, 1H), 3.33 (s, 3H), 3.44 (m, 2H), 3.64 (dd, 1H, J = 5.4, 9.0 Hz), 3.92 (d, 1H, J = 10.2 Hz), 3.99 (t, 1H, J = 9.0 Hz), 4.58 (t, 2H, J = 11.7 Hz), 4.66 (ABq, $\Delta\delta$ = 0.45 ppm, 2H, J = 11.7 Hz), 4.73 (d, 2H, J = 12.9 Hz), 4.77 (d, 2H, J = 10.8 Hz), 4.95 (m, 2H), 5.70 (m, 1H), 7.26 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 34.74, 55.24, 70.73, 72.14, 73.41, 74.85, 75.96, 78.45, 78.56, 80.50, 82.80, 97.97, 116.73, 127.62 – 128.56 (several lines), 136.09, 138.41, 138.61, 138.78.

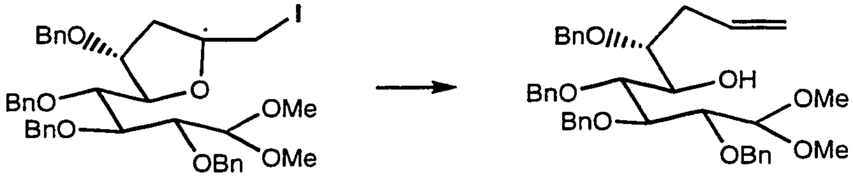
III.4.12 Synthesis of Iodo THF (III-39)



(III-38) **(III-39)**

The general iodoetherification procedure was applied to pyranoside alkene **(III-38)** (1.09 g, 1.84 mmol), using IDCP (2.5 g, 5.33 mmol) and MeOH (0.50 mL, 15.3 mmol). Flash chromatography of crude residue gave syrup **(III-39)**. $R_f = 0.40$ (Acetone : $CHCl_3$ = 1 : 99); ^{1}H NMR ($CDCl_3$) δ 1.98 (m, 1H), 2.17 (m, 1H), 3.18 (m, 2H), 3.22 (s, 3H), 3.45 (s, 3H), 3.64 (m, 1H), 3.78 (m, 1H), 4.07 (m, 1H), 4.23 (m, 2H), 4.45 (m, 2H), 4.55 – 4.70 (m, 4H), 4.79 – 4.93 (m, 3H), 7.28 (m, 20H); ^{13}C NMR (CDCl3) δ 8.37, 10.48, 37.45, 39.05, 54.07, 54.24, 71.38, 71.65, 73.98, 74.06, 75.06, 75.45, 75.59, 77.98, 78.35, 79.28, 79.92, 80.17, 80.31, 80.69, 85.49, 86.41, 105.44, 105.54, 127.61 – 128.57 (several lines), 137.90, 138.56, 139.16.

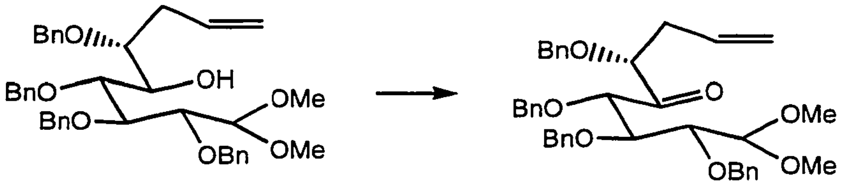
III.4.13 Synthesis of Hydroxy Alkene (III-40)



(III-39) **(III-40)**

Compound **(III-39)** was dissolved in 95% ethanol (25 mL) and stirred with freshly activated powdered zinc (7 g) at reflux for 1 h. The suspension was then diluted with ether and filtered through a short column of florisil. Concentration of the filtrate in vacuo followed by flash chromatography of the residual, dark brown oil afforded hydroxy alkene **(III-40)** (0.87 g, 76% after two steps). $R_f = 0.6$ (EtOAc : P.E = 20 : 80); ^{1}H NMR (CDCl3) δ 2.44 (m, 2H), 3.28 (d, 1H, J = 4.5 Hz), 3.34 (s, 3H), 3.44 (s, 3H), 3.65 (m, 1H), 3.86 (dd, 1H, J = 4.8, 6.0 Hz), 3.94 (dd, 1H, J = 4.2, 5.7 Hz), 4.08 (dd, 1H, J = 4.8, 10.8 Hz), 4.15 (t, 1H, J = 4.5 Hz), 4.51 (d, 1H, J = 5.4 Hz), 4.62 (s, 2H), 4.63 (d, 2H, J = 10.2 Hz), 4.76 (s, 2H), 4.86 (ABq, Δδ = 0.19 ppm, 2H, J = 11.4 Hz), 5.15 (m, 2H), 5.92 (m, 1H), 7.38 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 34.47, 54.93, 56.10, 71.82, 72.51, 72.79, 74.43, 77.13, 78.80, 78.89, 79.83, 106.07, 116.94, 127.57 – 128.67 (several lines), 135.62, 138.38, 138.51, 138.79, 138.85.

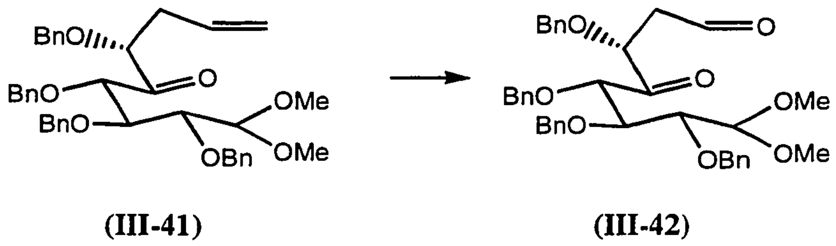
III.4.14 Synthesis of Keto Alkene (III-41)



(III-40) **(III-41)**

The general procedure for Swern's oxidation of alcohol was applied to **(III-40)** (1.1 g, 3.4 mmol), using DMSO (0.49 mL, 7.0 mmol), oxalyl chloride (0.5 mL, 5.8 mmol) and Et_3N (1.6 mL, 11.7 mmol). Flash chromatography of the crude product gave ketone **(III-41)** (1.04 g, 95%). $R_f = 0.7$ (EtOAc : P.E = 20 : 80); ^1H NMR ($CDCl_3$) δ 2.29 (m, 2H), 3.23 (s, 3H), 3.34 (s, 3H), 3.74 (dd, 1H, J = 4.2, 6.0 Hz), 4.08 (m, 3H), 4.39 (ABq, $\Delta\delta = 0.05$ ppm, 2H, J = 11.7 Hz), 4.45 (d, 1H, J = 6.3 Hz), 4.50 (ABq, $\Delta\delta = 0.04$ ppm, 2H, J = 11.7 Hz), 4.58 (ABq, $\Delta\delta = 0.24$ ppm, 2H, J = 11.7 Hz), 4.62 (d, 1H, J = 5.1 Hz), 4.72 (ABq, $\Delta\delta = 0.16$ ppm, 2H, J = 11.7 Hz), 4.99 (m, 2H), 5.68 (m, 1H), 7.33 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 34.14, 54.33, 55.74, 71.63, 73.38, 74.12, 74.25, 78.01, 79.42, 80.20, 81.19, 105.42, 117.62, 127.53 – 128.69 (several lines), 134.16, 137.94, 138.13, 138.41, 138.99, 207.13.

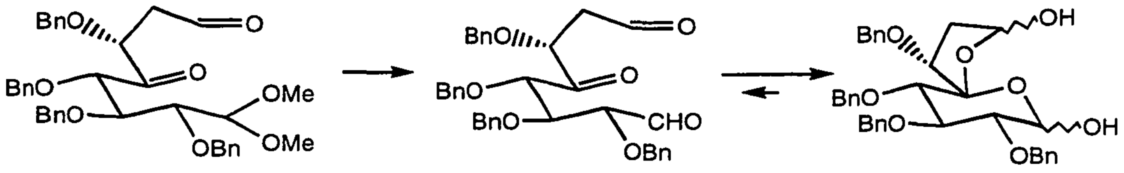
III.4.15 Synthesis of Keto Aldehyde (III-42)



(III-41) **(III-42)**

O_3 was bubbled at -78 ° C, through a solution of **(III-41)** (0.62 g, 1.0mmol) in a mixture of CH_2Cl_2 (5 mL) and MeOH (1 mL). The progress of the reaction was followed by tlc upon disappearance of starting material. The reaction vessel was purged with argon, and the reaction mixture warmed to rt. Methanol (4 mL) and Ph_3P (0.6g, 2.3 mmol) were then added and stirring continued under an argon atmosphere for 1h. Concentration of the reaction mixture followed by flash chromatography of the residual slurry afforded the keto-aldehyde derivative **(III-42)** (0.54 g, 85%). R_f = 0.30 (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.34 (m, 2H), 3.17 (s, 3H), 3.32 (s, 3H), 3.64 (dd, 1H, J = 3.0, 6.6 Hz), 3.99 (dd, 1H, J = 3.0, 4.8 Hz), 4.28 (ABq, $\Delta\delta$ = 0.05 ppm, 2H, J = 11.7 Hz), 4.28 (d, 1H, J = 10.8 Hz), 4.49 (ABq, $\Delta\delta$ = 0.11 ppm, 2H, J = 11.7 Hz), 4.52 (ABq, $\Delta\delta$ = 0.29 ppm, 2H, J = 12.0 Hz), 4.61 (ABq, $\Delta\delta$ = 0.32 ppm, 2H, J = 11.1 Hz), 4.62 (d, 1H, J = 5.1 Hz), 7.26 (m, 20H), 9.36(s, 1H); ^{13}C NMR (CDC_{l3}) δ 43.38, 54.21, 55.88, 72.11, 72.86, 73.89, 77.29, 77.43, 78.80, 79.92, 105.36, 127.60 - 128.81 (several lines), 137.74, 137.93, 137.67, 138.68, 200.07, 205.40.

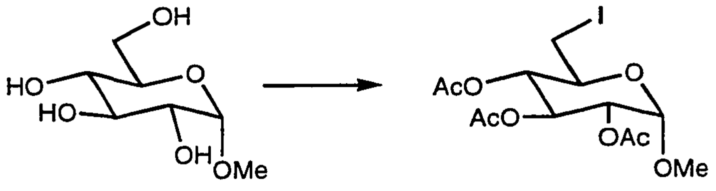
III.4.16 Synthesis of Tricarbonyl Precursor (III-24)



(III-42) **(III-24a)** **(III-24b)**

9M HCl (4.5 mL) was added to a solution of the keto-aldehyde **(III-42)** (0.24 g, 0.39 mmol) in THF (13.5 mL). The reaction mixture was stirred at rt for 1h, then carefully neutralized by addition of saturated aqueous $NaHCO_3$. The resulting mixture was extracted with ether (3 x) and the combined organic phase washed with brine. The organic layer was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Flash chromatography of the crude product provided recovered **(III-42)** (0.04 g) and **(III-24)** (0.16 g, 86% base on recovered **(III-42)**) white solid. $R_f = 0.45$ (EtOAc : P.E = 50 : 50); ^{1}H NMR ($CDCl_3$) δ 1.26(m, 2H), 1.75 – 2.60 (m, 2H), 3.46 (m, 1H), 3.77 – 4.07 (m, 3H), 4.45 - 4.97 (m, 8H), 5.13 - 5.48 (m, 2H), 7.26 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 39.80, 40.54, 73.15, 73.42, 74.67, 74.77, 74.90, 75.52, 75.66, 76.09, 76.17, 78.52, 79.21, 81.94, 82.24, 82.98, 83.19, 84.35, 84.74, 94.15, 94.52, 97.51, 98.06, 106.21, 107.91, 127.46 - 128.77 (several lines), 137.56, 137.69, 137.92, 138.62, 138.97, 138.81.

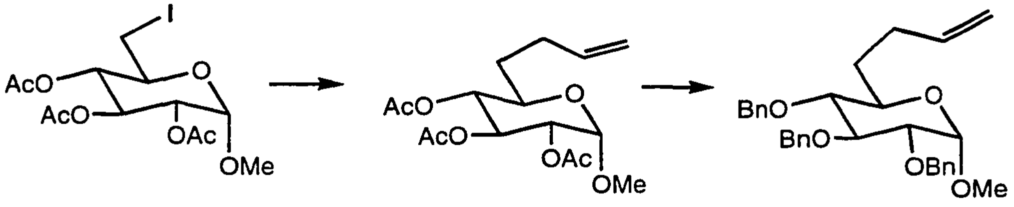
III.4.17 Synthesis of Methyl 2,3,4,-tri-O-acetyl 6-deoxy-6-iodo-α-D-glucopyranoside (III-43)



(I-38) **(III-43)**

Toluene (50 mL) was removed by using a Dean-Stark trap, from a mixture of **(I-38)** (10.0 g, 51.5 mmol), Ph_3P (30.5 g, 115.0 mmol) and imidazole (16.8 g, 238.0 mmol) in toluene (450 mL). CH_3CN (200 mL) was added to the residual solution. The solution was cooled to 60 °C, I_2 (28.0 g, 108.0 mmol) was added in small portions. The reaction mixture was refluxed for 2 h, then cool to rt. The solution was extracted with water (2 X 50 mL). The combined aqueous phase was washed by toluene (20 mL), concentrated *in vacuo*, and the crude residue was dried by removal of the toluene-water azeotrope. Acetic anhydride (52.5 g, 102.0 mmol), 0.5 mL pyridine and 4-dimethylaminopyridine (0.50 g, 4.1 mmol) were added to a solution of crude residue in EtOAc (250 mL). After stirring for 3 h, methanol (75 mL) was added and the reaction mixture evaporated *in vacuo*. Flash chromatography of crude product gave **(III-43)** (16.6 g, 75 % from **(I-38)**). $R_f = 0.60$ (EtOAc : P.E = 50 : 50); ^1H NMR ($CDCl_3$) δ 2.01 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 3.14 (dd, 1H, J = 8.4, 11.1 Hz), 3.31 (dd, 1H, J = 2.4, 11.1 Hz), 3.84 (s, 3H), 3.80 (m, 1H), 4.87 (m, 2H), 4.97 (d, 1H, J = 3.6 Hz), 5.47 (t, 1H, J = 9.9 Hz); ^{13}C NMR ($CDCl_3$) δ 20.98, 55.99, 68.90, 69.92, 71.16, 72.73, 76.66, 96.90, 169.67, 170.02, 170.11.

III.4.18 Synthesis of Pyranoside Alkene (III-26)

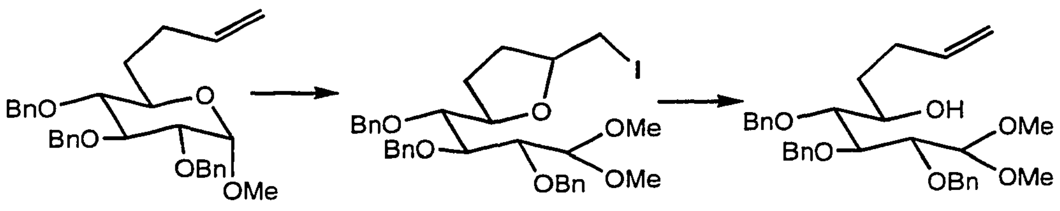


(III-43) **(III-43-1)** **(III-26)**

A solution of **(III-43)** (6.9 g, 16.0 mmol), AIBN (0.39 g, 2.4 mmol) and allyl tributyltin (10.6 g, 9.92 mL, 32.0 mmol) in benzene (64 mL) was purged with N_2 for 15 min. The reaction mixture was heated at reflux for 16 h. Saturated aqueous KF solution (50 mL) was then added and the mixture was extracted with ether (3 x). The combined organic phase was dried (Na_2SO_4), filtered and evaporated *in vacuo*. Compound **(III-43-1)** (3.3 g, 60 %) was obtained after flash chromatography. $R_f = 0.30$ (EtOAc : P.E = 20 : 80); ^1H NMR ($CDCl_3$) δ 1.61 (m, 2H), 1.99 (s, 3H), 2.03 (s, 3H), 2.07 (s, 3H), 2.10 (m, 1H), 2.28 (m, 1H), 3.38 (s, 3H), 3.76 (dt, 1H, J = 3.3, 9.0 Hz), 4.86 (m, 3H), 5.01 (m, 2H), 5.43 (t, 1H, J = 9.6 Hz), 5.78 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.02, 29.52, 30.69, 55.50, 68.00, 70.54, 71.45, 72.67, 96.73, 115.31, 137.83, 169.89, 170.13, 170.24.

A 1M solution of NaOMe (2.0 mL) in methanol was added to a solution of **(III-43-1)** (3.3 g, 9.7 mmol) in 25 mL dry methanol. The reaction was followed by tlc. After stirring at rt for 2 h, 1M HCl in methanol was carefully added to neutralize the reaction mixture. The solvent was removed at reduced pressure. The crude residue was subjected to the standard benzylation procedure (section II.5.2) to afford **(III-26)** (3.15 g, 6.5 mmol, 67 % two steps). $R_f = 0.70$ (EtOAc : P.E = 20 : 80); ^1H NMR ($CDCl_3$) δ 1.46 (m, 1H), 1.92 (m, 1H), 2.10 (m, 1H), 2.25 (m, 1H), 3.21 (t, 1H, J = 9.3 Hz), 3.38 (s, 3H), 3.53 (dd, 1H, J = 3.6, 12.9 Hz), 3.63 (dt, 1H, J = 2.1, 9.6 Hz), 3.98 (t, 1H, J = 9.3 Hz), 4.56 (d, 1H, J = 3.3 Hz), 4.75 (ABq, Δδ = 0.04 ppm, 2H, J = 12.0 Hz), 4.78 (ABq, Δδ = 0.29 ppm, 2H, J = 10.8 Hz), 4.92 (ABq, Δδ = 0.17 ppm, 2H, J = 10.8 Hz), 4.99 (m, 2H), 5.81 (m, 1H), 7.32 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 29.98, 31.23, 55.27, 69.80, 73.52, 75.44, 75.95, 80.40, 82.29, 98.00, 114.87, 127.71, 127.84, 128.00, 128.12, 128.24, 128.35, 128.52, 128.56.

III.4.19 Synthesis of Hydroxy Alkene (III-45)

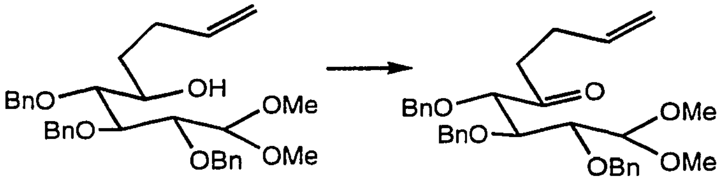


(III-26) **(III-44)** **(III-45)**

The standard iodoetherification procedure (section II.4.3) was applied to **(III-26)** (1.65 g, 3.4 mmol), using methanol as nucleophile. Compound **(III-44)** (1.80 g, 82.4 %) was obtained; R_f = 0.40 (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 1H), 1.96 (m, 2H), 2.12 (m, 1H), 3.15 (m, 2H), 3.27 (s, 3H), 3.47 (s, 3H), 3.58 (m, 1H), 3.68 (m, 1H), 3.91 (m, 2H), 4.05 (m, 1H), 4.51 (m, 1H), 4.64 (m, 1H), 4.71 - 4.88 (m, 4H), 7.26 (m, 15H); ^{13}C NMR (CDC13) δ 11.03, 19.90, 26.74, 27.84, 31.72, 33.04, 54.75, 54.90, 56.30, 73.53, 74.16, 74.98, 75.51, 76.93, 76.98, 77.37, 77.40, 77.44, 78.67, 78.89, 80.56, 80.80, 81.10, 81.48, 81.71, 83.08, 83.18, 84.96, 105.81, 105.89, 127.49 – 128.50 (several lines), 138.76, 139.10, 139.21.

Compound **(III-44)** (1.70 g, 2.63 mmol) was subjected to the standard the reductive elimination procedure (section II.5.3) to give **(III-45)** (1.25 g, 88%); $R_f = 0.45$ (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 1.46 (m, 1H), 1.61 (m, 1H), 2.06 (m, 1H), 2.17 (m, 1H), 2.93 (d, 1H, J = 3.9 Hz), 3.22 (s, 3H), 3.40 (s, 3H), 3.45 (dd, 1H, J = 4.8, 6.9 Hz), 3.67 (m, 2H), 3.85 (dd, 1H, J = 3.0, 4.8 Hz), 4.41 (d, 1H, J = 6.3 Hz), 4.56 (ABq, Δδ = 0.17 ppm, 2H, J = 11.7 Hz), 4.57 (t, 2H, J = 12.0 Hz), 4.52 (d, 1H, J = 6.0 Hz), 5.75 (m, 1H), 7.26 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 30.04, 32.84, 54.75, 56.63, 71.24, 73.44, 73.96, 74.34, 77.89, 77.94, 79.70, 105.99, 114.74, 127.77, 127.85, 127.90, 128.21, 128.41, 128.47, 128.51, 128.59, 138.06, 138.27, 138.81.

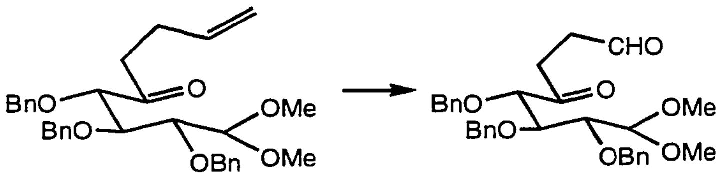
III.4.20 Synthesis of Keto Alkene (III-46)



(III-45) **(III-46)**

The standard Swern's oxidation procedure (section II.4.5) was applied to hydroxy alkene **(III-45)** (1.14g, 2.2 mmol). Compound **(III-46)** (1.07 g, 94 %) was obtained. $R_f = 0.55$ (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.14 (m, 2H), 2.57 (m, 2H), 3.34 (s, 3H), 3.41 (s, 3H), 3.73 (dd, 1H, J = 4.2, 6.0 Hz), 4.04 (m, 2H), 4.46 (d, 1H, J = 5.7 Hz), 4.60 (ABq, Δδ = 0.22 ppm, 2H, J = 11.7 Hz), 4.64 (ABq, Δδ = 0.15 ppm, 2H, J = 10.8 Hz), 4.69 (ABq, Δδ = 0.25 ppm, 2H, J = 11.1 Hz), 4.93 (m, 2H), 5.70 (m, 1H), 7.32 (m, 15H); ^{13}C NMR (CDCl$_3$) δ 27.43, 39.35, 54.87, 56.02, 73.32, 74.30, 74.81, 78.08, 80.01, 83.10, 105.63, 114.96, 127.45, 127.78, 127.93, 128.15, 128.18, 128.26, 128.37, 128.47, 137.48, 137.67, 138.11, 138.64, 209.21.

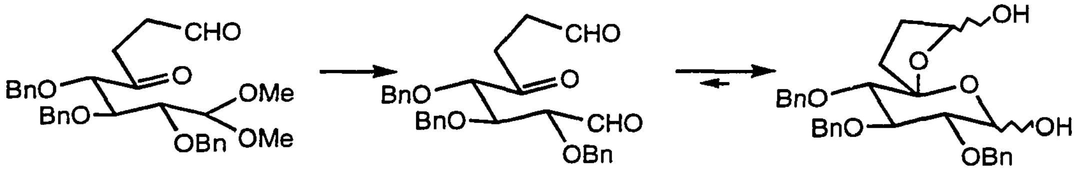
III.4.21 Synthesis of Keto Aldehyde (III-47)



(III-46) **(III-47)**

Keto alkene **(III-46)** (0.88 g, 1.7 mmol) was subjected to the identical ozonolysis procedure that was used for preparation of **(II-9)** (section II.4.11). Compound **(III-47)** (> 95%) was obtained. R$_f$ = 0.30 (EtOAc : P.E = 20 : 80); ^{1}H NMR (CDCl$_3$) δ 2.19 (m, 1H), 2.40 (m, 1H), 2.57 (m, 1H), 2.70 (m, 1H), 3.23 (s, 3H), 3.32 (s, 3H), 3.64 (dd, 1H, J = 3.9, 6.0 Hz), 3.93 (t, 1H, J = 4.5 Hz), 4.04 (d, 1H, J = 4.2 Hz), 4.37 (t, 2H, J = 5.1 Hz), 4.39 (s, 1H), 4.56 (ABq, Δδ = 0.05 ppm, 2H, J = 11.4 Hz), 4.68 (ABq, Δδ = 0.05 ppm, 2H, J = 11.1 Hz), 7.21 (m, 15H), 9.52 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 32.59, 37.33, 54.63, 55.90, 73.00, 74.09, 74.43, 77.66, 80.05, 82.16, 105.42, 127.41, 127.82, 127.86, 128.12, 128.17, 128.37, 128.42, 137.58, 137.85, 200.76, 207.43.

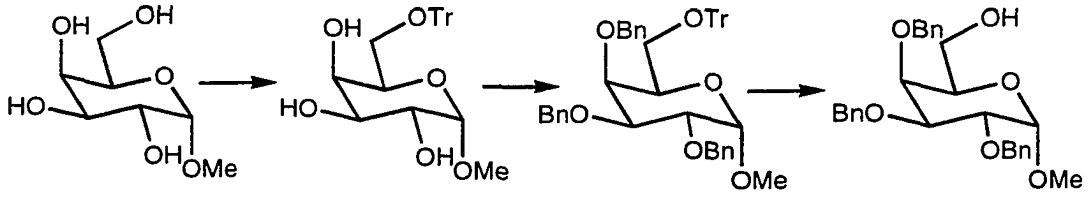
III.4.22 Synthesis of Tricarbonyl Precursor (III-25)



(III-47) **(III-25a)** **(III-25b)**

The hydrolysis procedure for preparation of **(II-1)** (section II.4.12) was applied to **(III-47)** (0.69 g, 1.33 mmol) to give **(III-25)** (0.60 g, 91 %). ^{1}H NMR ($CDCl_3$) δ 1.92 (m, 2H), 2.13 (m, 2H), 3.51 (m, 2H), 3.95 (m, 1H), 4.63 (m, 2H), 4.80 (m, 2H), 4.94 (m, 3H), 5.24 (m, 1H), 5.61 (m, 1H), 7.27 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 28.32, 29.83, 30.70, 31.41, 31.96, 32.42, 33.04, 60.57, 73.88, 74.77, 74.82, 75.33, 75.39, 75.46, 75.59, 75.65, 75.87, 76.04, 77.80, 79.48, 80.06, 80.10, 80.47, 81.04, 81.90, 81.98, 82.93, 83.56, 93.05, 93.37, 94.68, 100.10, 100.50, 107.06, 107.18, 107.34, 127.42, 127.54, 127.63, 127.88, 127.98, 128.12, 128.19, 128.32, 128.54, 128.63, 137.18, 137.53, 137.82, 138.24, 138.33, 138.39, 138.54, 138.61.

III.4.23 Synthesis of Methyl 2,3,4-tri-O-benzyl-galactopyranoside (III-48)



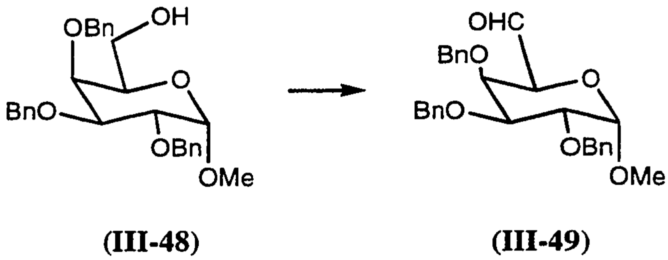
(III-29) **(III-29-1)** **(III-29-2)** **(III-48)**

A solution of compound **(III-29)** (10.8 g, 50.9 mmol), $(C_6H_5)_3CCl$ (28.4 g, 102.0 mmol), dimethylaminopyridine (DMAP) (0.62 g, 5.1 mmol) and Et_3N (TEA) (15.6 mL, 11.3 g, 112.0 mmol) in dry DMF (100 mL) was stirred at rt for 18 h. MeOH (5 mL) was added to the reaction mixture, and the volatile removed *in vacuo*. The crude residue was purified by flash chromatography to yield **(III-29-1)** (20.0 g, 85 %). R_f = 0.50 (EtOAc : MeOH = 90 : 10); ^{1}H NMR ($CDCl_3$) δ 3.29 (m, 1H), 3.38 (s, 3H), 3.40 (m, 1H), 3.72 (m, 4H), 3.80 (m, 2H), 3.89 (d, 1H, J = 3.0 Hz), 3.75 (d, 1H, J = 3.6 Hz), 7.23 (m, 10H), 7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 36.49, 55.19, 63.43, 69.43, 69.88, 70.89, 86.83, 99.64, 127.02, 127.83, 128.69.

Compound **(III-29-1)** (19.8 g, 45.4 mmol) was subjected the general benzylation reaction (section II.4.2) to give **(III-29-2)** (25.7 g, 80 %). R_f = 0.60 (EtOAc : P . E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 3.14 (dd, 1H, J = 6.6, 9.6 Hz), 3.35 (s, 3H), 3.40 (dd, 1H, J = 6.3, 9.3 Hz), 3.70 (t, 1H, J = 6.3 Hz), 3.86 (m, 2H), 3.96 (dd, 1H, J = 3.3, 10.2 Hz), 4.56 (ABq, $\Delta\delta$ = 0.20 ppm, 2H, J = 11.4 Hz), 4.73 (ABq, $\Delta\delta$ = 0.14 ppm, 2H, J = 12.3 Hz), 4.78 (ABq, $\Delta\delta$ = 0.15 ppm, 2H, J = 12.0 Hz), 4.81 (d, 1H, J = 11.1 Hz), 7.32 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 55.35, 63.43, 69.80, 73.55, 73.75, 74.83, 75.93, 79.33, 87.16, 97.57, 98.88, 127.24 – 128.85 (several lines), 138.77, 138.81, 139.16, 144.21.

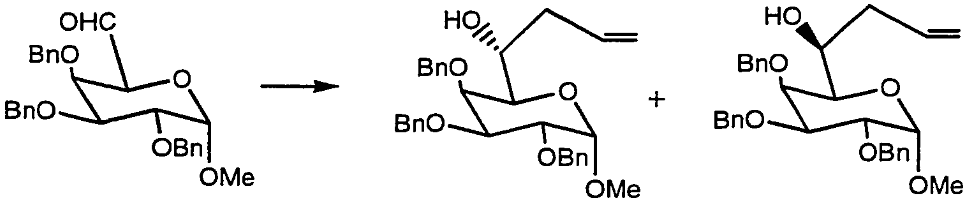
The **(III-29-2)** (23.2 g, 32.9 mmol) was dissolved in 20 % aqueous HOAc (100 mL). The reaction mixture was refluxed for 4 h, at which time the volatile was removed *in vacuo*. Flash chromatography of the residue gave **(III-48)** (13.5 g, 88 %); R_f = 0.40 (EtOAc : P . E = 30 : 70); ^{1}H NMR ($CDCl_3$) δ 2.21 (br, 1H), 3.30 (s, 3H), 3.43 (dd, 1H, J = 7.8, 14.1 Hz), 3.66 (dd, 1H, J = 7.8, 13.8 Hz), 3.67 (s, 1H), 3.82 (d, 1H, J = 2.4 Hz), 3.89 (dd, 1H, J = 2.7, 12.9 Hz), 4.01 (dd, 1H, J = 3.6, 10.2 Hz), 4.06 (dd, 1H, J = 7.2, 14.4 Hz), 4.66 (d, 1H, J = 4.2 Hz), 4.72 (ABq, Δδ = 0.15 ppm, 2H, J = 11.7 Hz), 4.75 (ABq, Δδ = 0.34 ppm, 2H, J = 11.4 Hz), 4.77 (ABq, Δδ = 0.14 ppm, 2H, J = 11.7 Hz) 7.31 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 14.29, 55.43, 62.42, 70.46, 73.66, 74.57, 75.28, 76.59, 79.20, 98.91, 127.66 – 128.60 (several lines), 138.32, 138.53, 138.82.

III.4.24 Synthesis of Tri-O-benzyl-galacto Aldehyde (III-49)



The standard Swern's oxidation procedure (section II.4.5) was applied to **(III-48)** (3.7 g, 7.9 mmol). Compound **(III-49)** (quantity recovered) was obtained. R_f = 0.60 (EtOAc : P . E = 30 : 70); ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 3H), 3.61 (m, 1H), 3.90 (m, 2H), 4.04 (s, 1H), 4.47 – 5.04 (m, 7H), 7.28 (m, 15H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.36, 55.46, 62.87, 73.37, 74.99, 75.72, 76.70, 78.96, 99.00, 127.62 – 128.61 (several lines), 137.91 – 138.81 (several lines), 200.49.

III.4.25 Synthesis of Homo Allylic Alcohol (III-28)



(III-49) **(III-28)** **(III-50)**

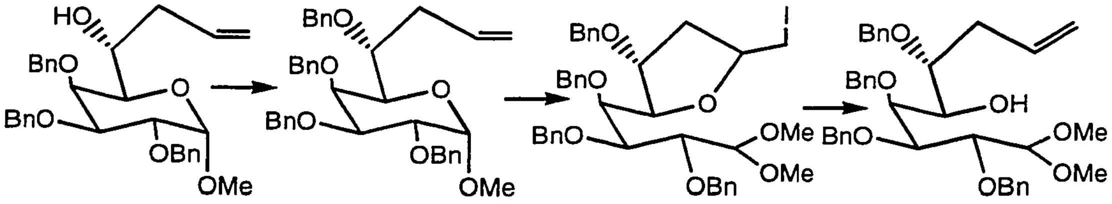
The aldehyde **(III-49)** from last step was treated with tin powder (1.88 g, 15.9 mmol, 100 mesh) and allyl bromide (2.06 mL, 2.88 g, 23.8 mmol) according to the procedure described for the preparation of compound **(II-6)** (section II.4.7). Flash chromatography of the residue afforded **(III-28)** (3.2 g, 74 %) and **(III-50)** (0.26 g, 6 %) in a ratio of 12 : 1.

For major product **(III-28)**: $R_f = 0.60$ (EtOAc : P . E = 30 : 70); ^{1}H NMR ($CDCl_3$) δ 1.48 (br, 1H), 1.96 (m, 1H), 2.41 (m, 1H), 3.25 (s, 3H), 3.29 (m, 1H), 3.66 (ddd, 1H, J = 3.0, 8.4, 11.7 Hz), 3.83 (dd, 1H, J = 2.7, 10.2 Hz), 3.97 (dd, 1H, J = 3.6, 10.2 Hz), 4.05 (d, 1H, J = 1.8 Hz), 4.56 (d, 1H, J = 5.4 Hz), 4.69 (ABq, $\Delta\delta$ = 0.18 ppm, 2H, J = 11.7 Hz), 4.72 (ABq, $\Delta\delta$ = 0.09 ppm, 2H, J = 12.0 Hz), 4.76 (ABq, $\Delta\delta$ = 0.29 ppm, 2H, J = 11.7 Hz), 5.01 (m, 2H), 5.70 (m, 1H), 7.25 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 38.44, 55.55, 68.34, 72.32, 73.49, 73.70, 74.06, 74.62, 76.47, 79.43, 99.12, 118.49, 127.65 – 128.62 (several lines), 134.59, 138.65, 138.77, 138.93.

For minor product **(III-50)**: $R_f = 0.50$ (EtOAc : P . E = 30 : 70); ^{1}H NMR ($CDCl_3$) δ 2.09 (t, 2H, J = 6.6 Hz), 3.34 (s, 3H), 3.48 (d, 1H, J = 4.8 Hz), 3.81 (dd, 1H, J = 6.0, 11.1 Hz), 3.90 (m, 2H), 4.03 (dd, 1H, J = 3.0, 10.5 Hz), 4.71 (d, 1H, J = 3.9 Hz), 4.73 (ABq, $\Delta\delta$ =

0.14 ppm, 2H, J = 12.0 Hz), 4.75 (ABq, Δδ = 0.27 ppm, 2H, J = 11.7 Hz), 4.88 (ABq, Δδ = 0.32 ppm, 2H, J = 11.1 Hz), 4.96 (m, 2H), 5.74 (m, 1H), 7.30 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 37.44, 55.65, 71.12, 71.38, 73.72, 74.00, 74.67, 76.36, 77.23, 79.52, 99.05, 117.50, 127.69 – 128.62 (several lines), 134.60, 138.04, 138.51, 138.83.

III.4.26 Synthesis of Tetra-O-benzyl-galacto Alkene (III-51)



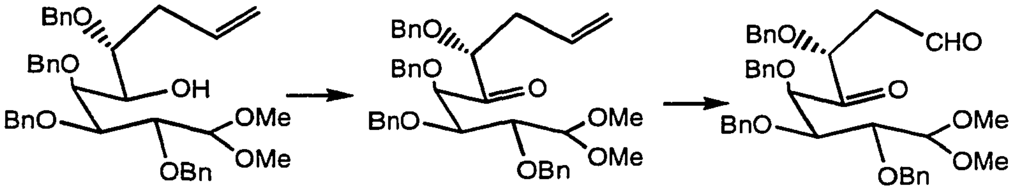
(III-28) **(III-28-1)** **(III-28-2)** **(III-51)**

Application of the general benzylation procedure (section II.4.2) to **(III-28)** (3.1 g, 6.2 mmol) yielded **(III-28-1)** (3.3 g, 90 %); R_f = 0.60 (EtOAc : P . E = 10 : 90); ^{1}H NMR ($CDCl_3$) δ 2.37 (m, 1H), 2.66 (m, 1H), 3.34 (s, 3H), 3.66 (d, 1H, J = 9.3 Hz), 3.81 (dt, 1H, J = 3.0, 4.5 Hz), 3.91 (dd, 1H, J = 2.4, 10.2 Hz), 4.04 (dd, 1H, J = 3.9, 9.9 Hz), 4.14 (d, 1H, J = 1.8 Hz), 4.39 (ABq, Δδ = 0.39 ppm, 2H, J = 10.8 Hz), 4.64 (d, 1H, J = 3.6 Hz), 4.72 (ABq, Δδ = 0.14 ppm, 2H, J = 12.0 Hz), 4.75 (ABq, Δδ = 0.55 ppm, 2H, J = 11.1 Hz), 4.76 (ABq, Δδ = 0.12 ppm, 2H, J = 11.7 Hz), 5.08 (m, 2H), 5.92 (m, 1H), 7.26 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 34.25, 55.81, 70.88, 71.50, 73.37, 73.63, 74.65, 75.25, 75.86, 76.39, 79.71, 99.30, 117.65, 127.50 – 128.48 (several lines), 134.23, 138.40, 138.68, 139.01, 139.20; Anal calcd for $C_{38}H_{42}O_6$: C, 76.74; H, 7.12. found: C, 76.38; H, 6.82.

The standard iodoetherification procedure (section II.4.3) was applied to alkene **(III-28-1)** (3.1 g, 5.2 mmol) and using MeOH as nucleophile. A mixture of iodo-THF **(III-28-2)** was obtained. $R_f = 0.55$ (EtOAc : P . E = 10 : 90);^{1}H NMR ($CDCl_3$) δ 1.71 (m, 1H), 2.15 (m, 1H), 3.21 (m, 2H), 3.30 (s, 3H), 3.42 (s, 3H), 3.80 (m, 3H), 3.97 (m, 1H), 4.03 (br, 1H), 4.34 (m, 3H), 4.41 (m, 2H), 4.65 (m, 2H), 4.94 (m, 2H), 7.26 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 8.80, 11.00, 14.32, 21.11, 37.82, 38.89, 53.62, 54.93, 55.04, 60.41, 71.13, 71.56, 72.74, 72.93, 73.74, 73.63, 74.55, 78.03, 78.62, 79.12, 79.29, 80.21, 80.94, 83.85, 85.41, 104.53, 104.66, 127.37 – 128.48 (several lines), 138.06, 138.13, 138.48, 139.10, 139.39.

The **(III-28-2)** from last step was treated according to the standard procedure for reductive elimnation condition (section II.4.4). Compound **(III-51)** (3.2 g, 98 % from **(III-28-1)**) was obtained. $R_f = 0.35$ (EtOAc : P . E = 10 : 90); ^{1}H NMR ($CDCl_3$) δ 2.50 (m, 1H), 2.68 (m, 1H), 3.33 (s, 3H), 3.36 (s, 3H), 3.62 (dt, 1H, J = 4.2, 8.7 Hz), 3.70 (t, 1H, J = 3.0 Hz), 3.88 (d, 1H, J = 9.0 Hz), 4.07 (br, 2H), 4.39 (ABq, Δδ = 0.45 ppm, 2H, J = 11.1 Hz), 4.43 (ABq, Δδ = 0.10 ppm, 2H, J = 11.7 Hz), 4.46 (d, 1H, J = 5.4 Hz), 4.75 (ABq, Δδ = 0.07 ppm, 2H, J = 11.1 Hz), 4.76 (ABq, Δδ = 0.20 ppm, 2H, J = 11.4 Hz), 5.10 (m, 2H), 5.93 (m, 1H), 7.28 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 34.37, 55.90, 70.98, 71.61, 73.47, 73.73, 74.72, 75.32, 75.95, 76.48, 79.82, 97.54, 99.38, 117.73, 127.53 – 128.58 (several lines), 134.33, 138.49, 138.77, 139.11.

III.4.27 Synthesis of Keto Aldehyde (III-53)

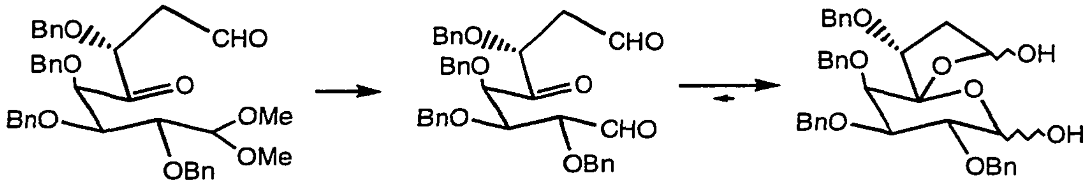


(III-51) **(III-52)** **(III-53)**

The general Swern's oxidation procedure (section II.4.5) was applied to **(III-51)** (3.1 g, 5.0 mmol). Ketone **(III-52)** (2.9 g, 93 %) was obtained. $R_f = 0.50$ (EtOAc : P . E = 10 : 90); ^{1}H NMR (CDCl$_3$) δ 2.28 (m, 1H), 2.46 (m, 1H), 3.29 (s, 3H), 3.37 (s, 3H), 3.42 (s, 1H), 3.51 (m, 1H), 3.76 (m, 1H), 4.05 (m, 1H), 4.22 (m, 2H), 4.45 (m, 3H), 4.59 (m, 2H), 4.78 (m, 2H), 5.00 (m, 2H), 5.75 (m, 1H), 7.26 (m, 20H); ^{13}C NMR (CDCl$_3$) δ 35.34, 54.65, 56.02, 71.98, 72.06, 74.60, 74.76, 78.91, 80.33, 80.44, 82.41, 97.51, 105.51, 117.64, 127.68 – 128.51 (several lines), 134.03, 137.76, 138.16, 138.35, 138.86.

The standard ozonolysis procedure that was used for preparation of compound (II-9) was applied to alkene **(III-52)** (1.5 g, 2.4 mmol) to give dicarbonyl compound **(III-53)** (1.2 g, 80 %). $R_f = 0.60$ (EtOAc : P . E = 10 : 90); ^{1}H NMR (CDCl$_3$) δ 2.42 (ddd, 1H, J = 1.8, 8.1, 17.4 Hz), 2.71 (dd, 1H, J = 3.3, 17.4 Hz), 3.38 (s, 3H), 3.39 (s, 3H), 3.39 (m, 1H), 3.85 (t, 1H, J = 5.1 Hz), 4.11 (m, 2H), 4.37 (ABq, $\Delta\delta = 0.17$ ppm, 2H, J = 11.1 Hz), 4.42 (ABq, $\Delta\delta = 0.09$ ppm, 2H, J = 11.7 Hz), 4.45 (d, 1H, J = 2.1 Hz), 4.63 (ABq, $\Delta\delta =$ 0.13 ppm, 2H, J = 11.4 Hz), 4.68 (ABq, $\Delta\delta = 0.18$ ppm, 2H, J = 11.4 Hz), 7.26 (m, 20H), 9.43 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 44.45, 55.25, 55.88, 72.15, 72.52, 74.67, 75.26, 77.31, 78.90, 80.35, 81.72, 97.46, 105.74, 127.51 - 128.61 (several lines), 137.41, 137.59, 138.18, 138.58, 199.37, 208.27.

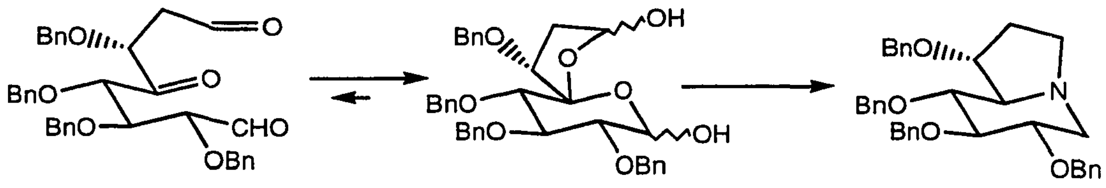
III.4.28 Synthesis of Tricarbonyl Precursor (III-27)



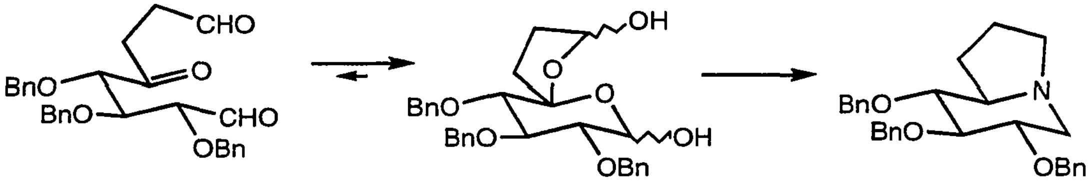
(III-53) **(III-27a)** **(III-27b)**

The general hydrolysis procedure that was used for the synthesis of **(II-1)** was applied to **(III-53)** (0.90 g, 1.4 mmol). Compound **(III-27)** (0.66 g, 77 %) was obtained. ^{1}H NMR ($CDCl_3$) δ 1.70, 1.84, 2.09, 2.24, 2.34 (all m, 2H), 3.17 (br, 2H), 3.56 (m, 1H), 3.64 (m, 1H), 3.90 (m, 1H), 4.05 - 4.26 (m, 3H), 4.36 (m, 1H), 4.54 (m, 1H), 4.66 (br, 1H), 4.75 - 5.04 (m, 3H), 5.07 - 5.60 (m, 2H), 7.28 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 36.58, 45.06, 62.19, 71.26, 72.09, 72.98, 73.36, 74.69, 74.80, 75.06, 75.21, 75.91, 77.46, 80.43, 80.88, 81.72, 83.13, 93.64, 94.27, 97.54, 100.87, 101.03, 108.68, 108.92, 127.29 - 128.84 (several lines), 137.89, 138.77, 138.84, 139.23, 139.35.

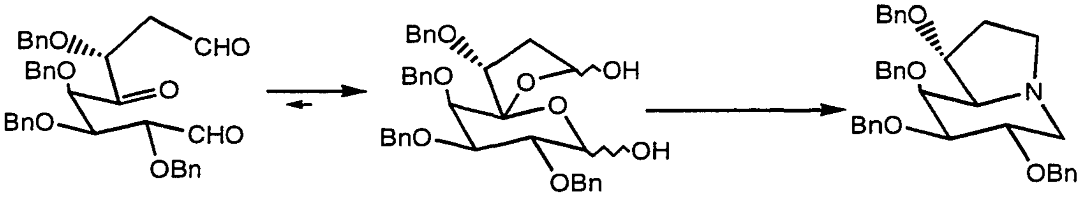
III.4.29 Triple Reductive Aminations



(III-24a) **(III-24b)** **(III-54)**



(III-25a) **(III-25b)** **(III-55)**



(III-27a) **(III-27b)** **(III-56)**

The standard triple reductive amination procedure that was used for preparation of the compound **(II-10)** (section II.4.13) was applied to the tricarbonyl precursors **(III-24)** (0.15 g, 0.25 mmol), **(III-25)** (0.15 g, 0.3 mmol) and **(III-27)** (0.20 g, 0.33 mmol). Analogues of castanospermine **(III-54)** (65 mg, 48%), **(III-55)** (0.054 g, 40 %) and **(III-56)** (0.063 g, 34 %) was obtained respectively.

For **(III-53)**; R_f = 0.55 (EtOAc : P.E = 50 : 50); ^{1}H NMR (C_6D_6) δ 1.70 (m, 1H), 1.88 (m, 1H), 2.10 (t, 1H, J = 10.2 Hz), 2.33 (dd, 1H, J = 8.1, 15.6 Hz), 2.42 (dd, 1H, J = 5.1, 9.3 Hz), 2.62 (t, 1H, J = 7.8 Hz), 3.06 (dd, 1H, J = 5.1, 7.8 Hz), 3.46 (t, 1H, J = 9.0 Hz), 3.64 (t, 1H, J = 8.7 Hz), 3.75 (m, 1H), 3.84 (m, 1H), 4.35 (ABq, 2H, Δδ = 0.09 ppm, 2H, J = 16.8 Hz), 4.51 (ABq, Δδ = 0.03 ppm, 2H, J = 6.0 Hz), 4.85 (ABq, Δδ = 0.38 ppm, 2H, J = 11.4 Hz), 4.91 (t, 2H, J = 12.3 Hz), 7.03 – 7.40 (m, 20H); ^{13}C NMR (C_6D_6) δ 32.49, 52.20, 54.45, 71.66, 72.94, 73.27, 74.81, 76.12, 80.28, 82.76, 82.87, 88.49, 127.76 – 128.90 (several lines), 139.76, 139.80, 140.04, 140.27.

For **(III-54)**; ^{1}H NMR (C_6D_6) δ 1.23 (m, 2H), 1.41 (m, 1H), 1.94 (m, 4H), 2.79 (td, 1H, J = 1.8, 8.4 Hz), 3.14 (dd, 1H, J = 5.4, 10.8 Hz), 3.37 (t, 1H, J = 8.7 Hz), 3.64 (t, 1H, J = 8.7 Hz), 3.81 (m, 1H), 4.53 (ABq, Δδ = 0.05 ppm, 2H, J = 11.7 Hz), 4.74 (ABq, Δδ = 0.16 ppm, 2H, J = 11.7 Hz), 5.00 (ABq, Δδ = 0.15 ppm, 2H, J = 11.1 Hz), 7.16 (m, 15H); ^{13}C NMR (C_6D_6) δ 23.17, 30.04, 54.00, 55.03, 68.12, 73.10, 74.96, 76.09, 80.79, 84.71, 88.32, 127.81, 127.92, 128.08, 128.20, 128.40, 128.71, 128.88, 129.02, 129.23, 139.90, 140.19, 140.44.

For **(III-55);** ^{1}H NMR (C_6D_6) δ 1.57 (m, 1H, H2), 1.99 (t, 2H, J = 10.2 Hz, H3, H5), 2.20 (m, 2H, H2, H8a), 2.79 (dd, 1H, J = 7.2, 8.4 Hz, H3), 3.19 (m, 1H, H5), 3.38 (dd, 1H, J = 3.0, 9.6 Hz, H7), 4.02 (br, 1H, H8), 4.20 (m, 2H, H1, H6), 4.22 (ABq, Δδ = 0.20 ppm, 2H, J = 11.7 Hz), 4.53 (ABq, Δδ = 0.14 ppm, 2H, J = 11.4 Hz), 4.59 (ABq, Δδ = 0.22 ppm, 2H, J = 11.7 Hz), 4.81 (ABq, Δδ = 0.52 ppm, 2H, J = 11.1 Hz), 7.27 (m, 20H); ^{13}C NMR (C_6D_6) δ 31.06, 52.72, 55.87, 72.03, 72.27, 73.75, 73.60, 73.34, 75.52, 77.00, 78.36, 86.18, 79.10, 127.84 – 128.91 (several lines), 139.67, 140.05, 140.19.

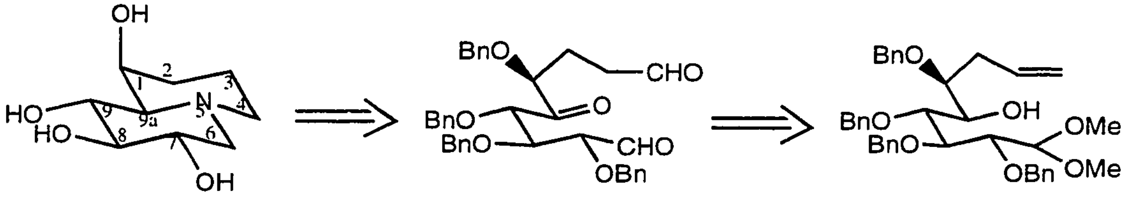
Chapter IV

Synthesis of Quinolizidine and Pyrrolizidine Systems

IV.1 Polyhydroxyquinolizidines – General Considerations

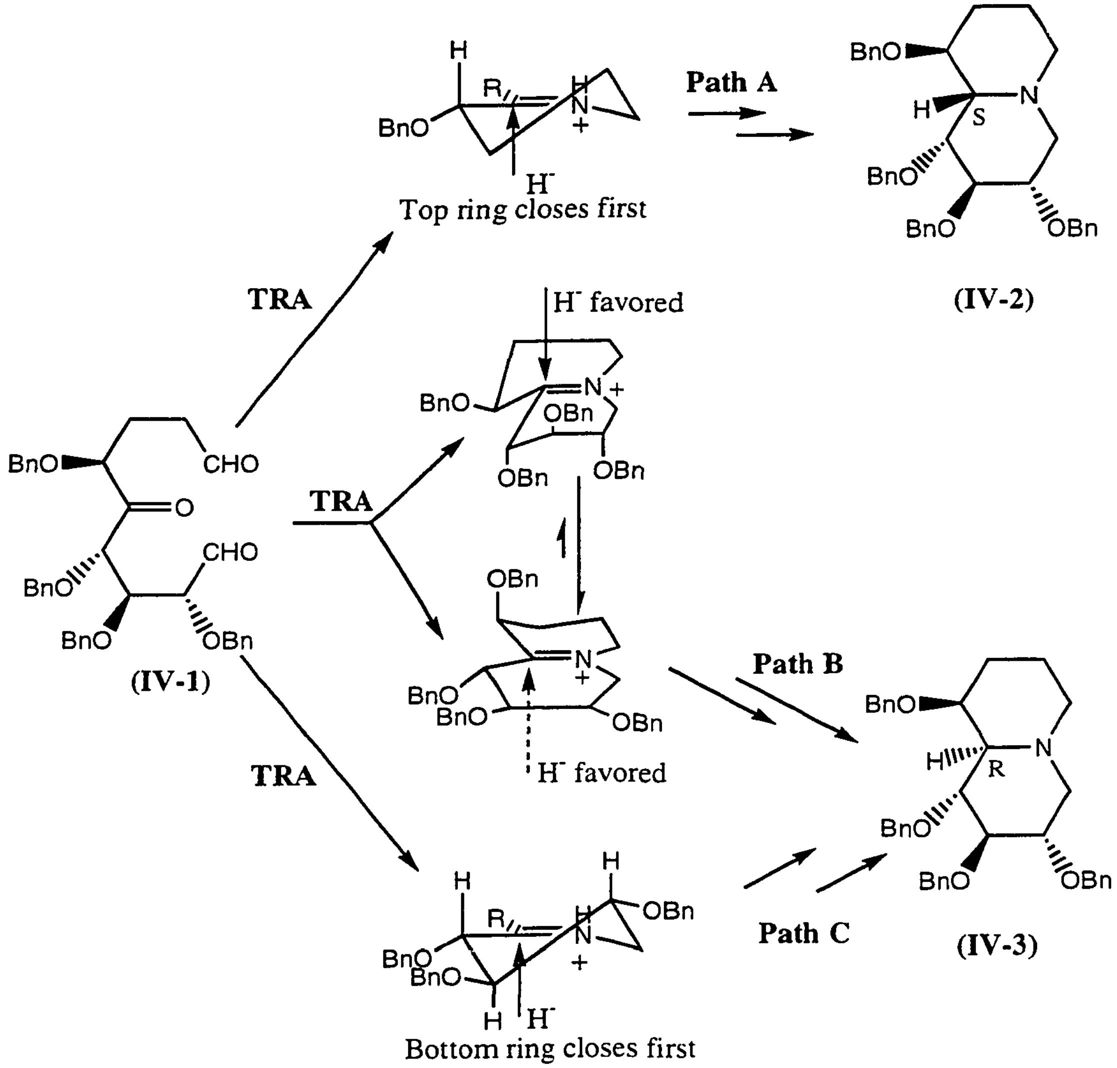
Application of the TRA strategy to the quinolizidines was next tested. The cyclization of the tricarbonyl precursor (**IV-1**) is interesting, because hydride reduction of the individual six membered iminium ions should give opposite results. Therefore if the rates of initial addition to both aldehydes, and the reduction formation of the six membered iminium ions were similar, the stereoselectivity would be expected to be low. However if the overall rate of formation of one of the two cyclic amines is much faster than the other, or a bicyclic iminium ion is involved (Path B), the stereoselectivity could be high.

Scheme IV-1.



(I-6) **(IV-1)** **(II-7)**

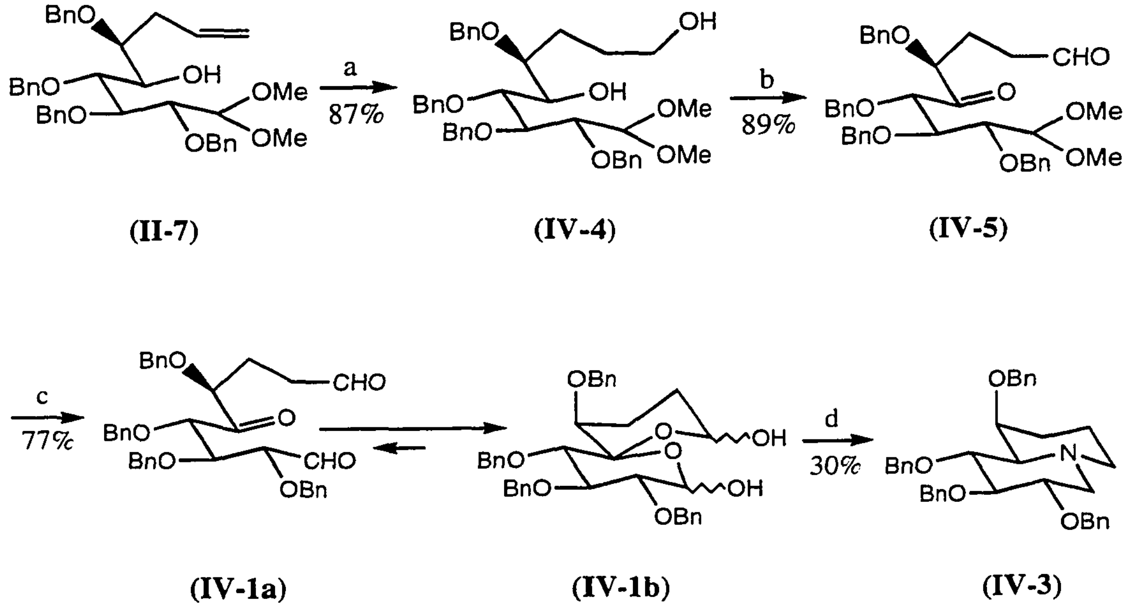
Scheme IV-2.



IV.2 Synthesis

The hydroboration of the previous obtained alkenyl acetal-alcohol **(II-7)** gave diol **(IV-4)**. Swern's oxidation of **(IV-4)**, followed by hydrolysis of the resulting keto-aldehyde **(IV-5)**, provided the tricarbonyl precursor. As for the previously prepared tricarbonyl compound, **(IV-1)** no evidence for the keto aldehyde tautomer **(IV-1a)** was observed. Instead, NMR data suggested a mixture of acetal diastereomers **(IV-1b)**. Application of the TRA conditions provided the tetra-O-benzyl polyhydroxyquinolizidine **(IV-3)** in 30 % yield as a single stereoisomer.

Scheme IV-3.



(II-7) **(IV-4)** **(IV-5)**

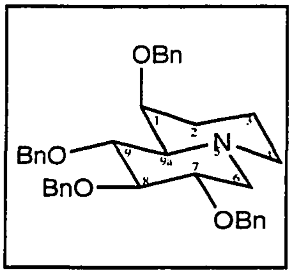
(IV-1a) **(IV-1b)** **(IV-3)**

Key: (a). 9-BBN, THF, then 30% H_2O_2, NaOH (3N); (b). Swern's oxidation; (c). THF—9M HCl; (d). 1.3(eq) NH_4HCO_2, 30 (eq) $NaCNBH_3$, MeOH.

COSY NMR was used to assign the protons of polyhydroxyquinolizidine **(IV-3)**. The configuration of newly formed chiral center was ascertained from the coupling constant between adjacent protons. H8 and H9 appeared as triplet at δ 3.64 and δ 4.12

ppm respectively, both with a J value of 9.0 Hz. The magnitude of the coupling constant suggests that H7, H8, H9 and H9a are all axial. Therefore the conformation of polyhydroxyquinolizidine **(IV-3)** was assigned as **Figure IV-1**.

Figure IV-1.



(IV-3)

Table IV-1. ^{1}H and ^{13}C data for **(IV-3)**

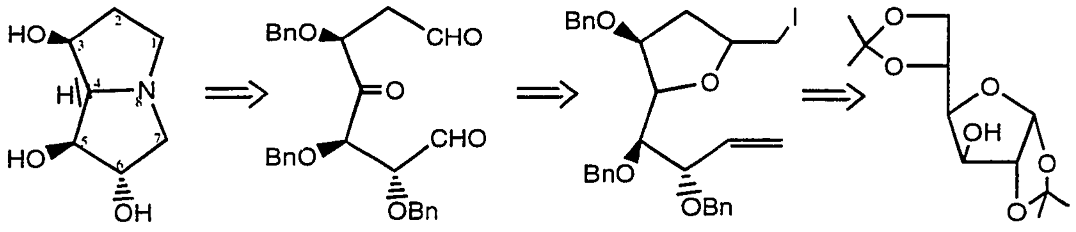
^{1}H		**^{13}C**	
H1	**3.91**	**C1,C7,C8,C9**	**70.76 or 71.95 or 73.09 or 75.44**
H2	**0.91** **1.91**	**C2**	**26.74**
H3	**1.13** **1.91**	**C3**	**20.52**
H4	**1.91** **2.70**	**C4**	**56.35**
H6	**1.91** **2.94**	**C6**	**59.74**
H7	**3.72**		
H8	**3.64**		
H9	**4.12**		
H9a	**1.91**	**C9a**	**68.99**

This stereochemical result is consistent with initial formation of the more substituented piperidine (**Path C**), or the reduction of a bicyclic iminium ion (**Path B**). It is conceivable that nucleophile addition to the aldehyde on the lower ring could be faster than the other aldehyde, because of the proximity of the electron withdrawing benzyloxy substituents.

IV.3 Polyhydroxypyrrolizidines – General Considerations

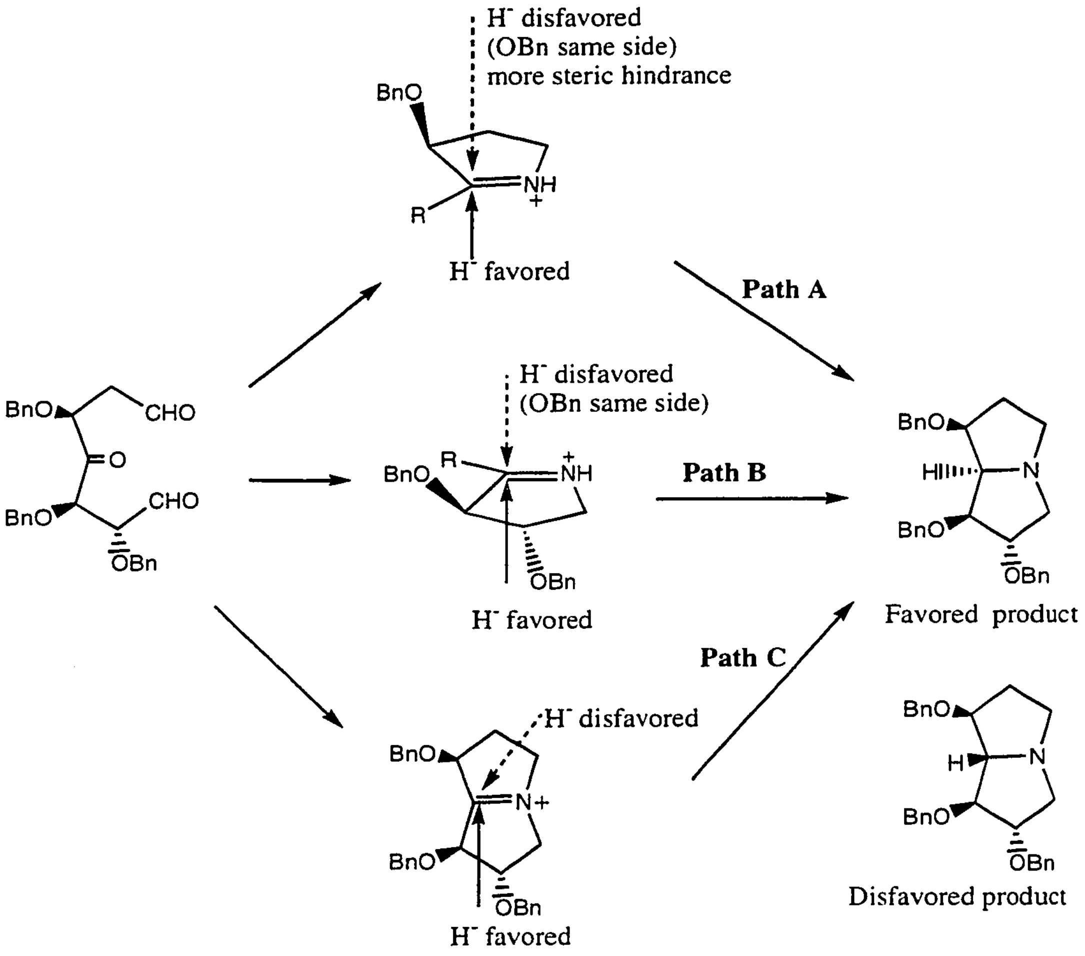
The synthesis of the pyrrolizidine ring system was also investigated. The TRA of the tricarbonyl precursor **(IV-6)** is expected to occur with high stereoselectivity since the reduction of all three possible iminium ion intermediates should proceed from the same direction (Schemes IV-4, IV-5). However there was concern that the formation of the [3.3.0] system might be very low yielding because of the low yield for the double reductive amination of the 1,4-dicarbonyl precursor **(II-28)**. (Scheme II-8)

Scheme IV-4.



(I-7) **(IV-6)** **(IV-7)** **(IV-8)**

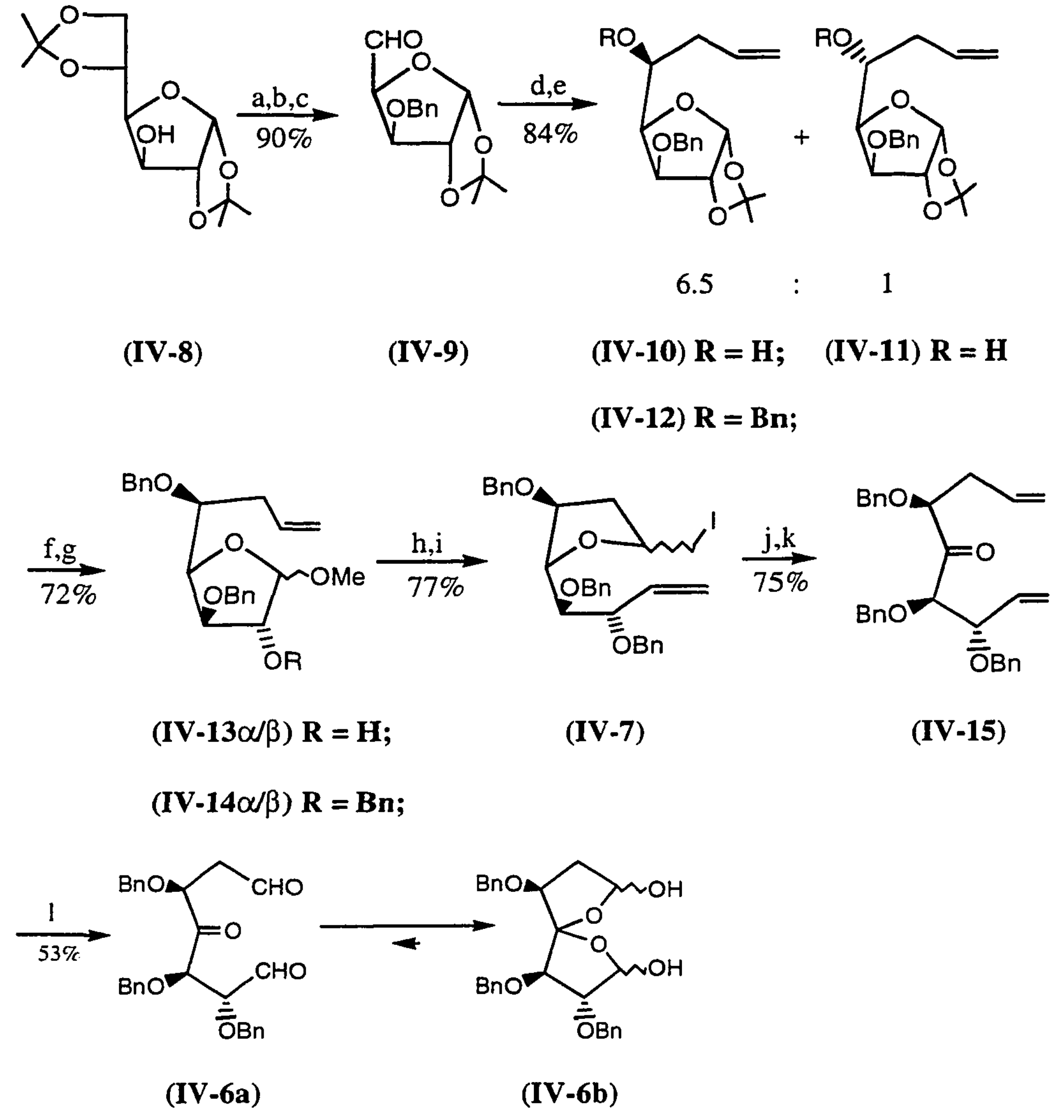
Scheme IV-5.


H⁻ disfavored
(OBn same side)
more steric hindrance
BnO
R
NH
+
H⁻ favored
Path A
BnO
CHO
O
BnO
CHO
OBn
H⁻ disfavored
(OBn same side)
BnO
R
+
NH
OBn
H⁻ favored
Path B
BnO
H
N
BnO
OBn
Favored product
Path C
H⁻ disfavored
BnO
N+
BnO
OBn
H⁻ favored
BnO
H
N
BnO
OBn
Disfavored product

IV.4 Synthesis

The mixture of the known alcohols **(IV-10)** and **(IV-11)** was obtained according the protocol developed by Danishefsky[47]. Thus the allylation of the aldehyde **(IV-9)** (three steps from 1,2,5,6-di-O-isopropyl D-glucofuranose **(IV-8)**), with allyl trimethylsilene and $TiCl_4$ gave **(IV-10)** and **(IV-11)** in ratio 6.5 : 1. Benzylation of the major alcohol, followed by methanolysis of the product under acidic conditions provided a mixture of methyl furanosides **(IV-13α/β)**. Benzylation of **(IV-13α/β)** afforded benzyl ether **(IV-14α/β)**. The anomeric configuration was assigned by 13C NMR comparisons with known furanoside derivatives.[51] The mixture **(IV-14α/β)** was treated with IDCP and water, and this was followed by the Wittg reaction on the resulting aldehyde. The two step operations yielded iodo THF's alkene **(IV-7)** in 76% overall yield. The compound **(IV-7)** was transformed to keto diene **(IV-15)** through Zn mediated reductive elimination, followed by Swern's oxidation of the resulting alcohol. The ozonolysis of **(IV-15)** gave tricarbonyl compound **(IV-6)**. As for previously obtained tricarbonyl compound no evidence of the keto aldehyde tautomer was observed. The NMR evidence was consistent with the acetal **(IV-6b)**.

Scheme IV-6.



(IV-8) (IV-9) (IV-10) R = H; (IV-11) R = H

(IV-12) R = Bn;

(IV-13α/β) R = H; (IV-7) (IV-15)

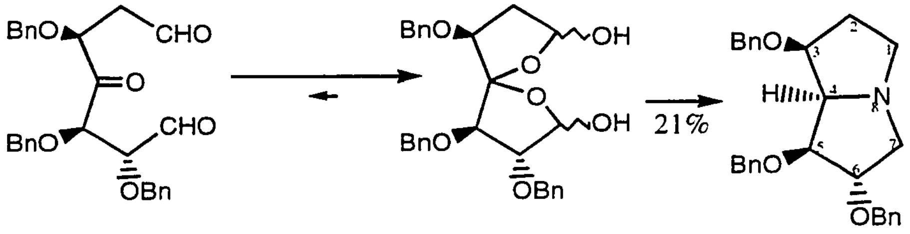
(IV-14α/β) R = Bn;

(IV-6a) (IV-6b)

Key: (a). BnBr, NaH, n-Bu$_4$NI, DMF(dry); (b). H_2SO_4, MeOH, H_2O; (c). $NaIO_4$, MeOH, H_2O; (d). $CH_2{=}CHCH_2Si(CH_3)_3$, $TiCl_4$, CH_2Cl_2(dry); (e). BnBr, NaH, n-Bu$_4$NI, DMF(dry); (f). HCl (gas) in Methanol; (g). BnBr, NaH, n-Bu$_4$NI, DMF (dry); (h). IDCP, CH_2Cl_2 (wet); (i). Wittg reaction; (j). Zn, EtOH (95%); (k). Swern's oxidation; (l) O_3, Ph_3P;

The TRA was carried out on **(IV-6)**. The major product **(IV-16)** was obtained in yield 21 %. An unidentified product was also obtained in a 15 % yield. The structure of **(IV-16)**) was assigned by ^{1}H NMR (1D & 2D), and ^{13}C NMR. The configuration of C_4 was determined by NOSEY. The observation of a nOe between one of the H1 protons and H3 and H4 ensured that H3 and H4 were cis.

Scheme IV-7.

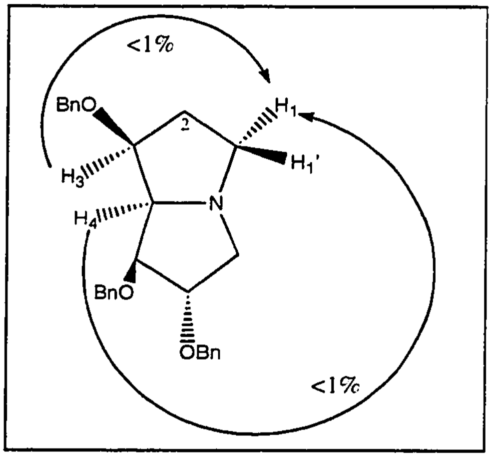


(IV-6a) **(IV-6b)** **(IV-16)**

Table IV-2 ^{1}H and ^{13}C data for (IV-16)

^{1}H		^{13}C	
H1	**2.71**	**C1**	**62.13**
	3.41		
H2	**1.35**	**C2**	**30.71**
	1.83		
H3	**3.66**	**C3,C5,C6**	**71.62 or 72.32 or 80.28**
H5	**3.61**		
H6	**3.84**		
H7	**2.75**	**C7**	**64.85**
	3.48		
H4	**3.92**	**C4**	**66.33**

Figure IV-2



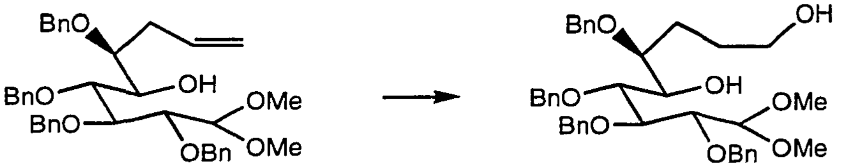
(IV-16)

Summary

The results for the pyrrolizidine and quinolizidine and indolizidine system indicate that it is possible to obtain high stereoselectivity in TRA cyclization on highly substituted substrates. For system which contain a piperidine ring, the stereoselectivity appears to be controlled by the stereochemistry of the substrates on the forming six membered ring. However, a mechanism involving a bicyclic iminium species can not be excluded. The yields of the TRA reaction are somewhat modest for the indolizidines (40 - 50 %), and lower for the quinolizidine (30 %) and pyrrolizidine (20 %) systems. The low yields in the latter cases might be an indication of a slower rate of formation of the associated iminium ion intermediates, which leads to increased formation of side products resulting from polyamination.

IV.5 Experimental

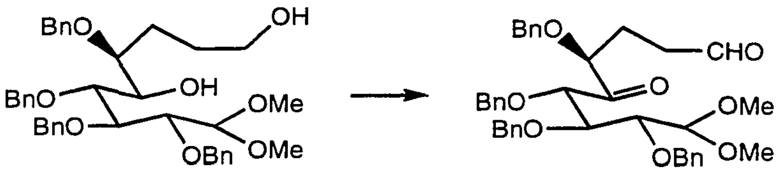
IV.5.1 Synthesis of Diol (IV-4)



(II-7) **(IV-4)**

A 0.5 M solution of 9-BBN (19.7 mL, 9.87 mmol) in THF was added to a solution of **(II-7)** (2.06 g, 3.29 mmol) in THF (70 mL) at 0°C. The reaction mixture was stirred at this temperature for 1.5 h, then warmed to rt for additional 18 h. The solution was cooled to 0°C, and a 1 : 1 mixture (30 mL) of 30 % H_2O_2 and 3N NaOH was added. The reaction solution was stirred for 30 min, then extracted with ether (3 x), combined organic solution, washed by brine, dried (Na_2SO_4), concentrated *in vacuo*. The crude residue was purified with flash chromatograph to afford **(IV-4)** (1.85 g, 87 %). $R_f = 0.40$ (EtOAc : P.E = 50 : 50); $[\alpha]_D$ +30.1 (c = 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 2H), 1.71 (m, 2H), 3.25 (s, 3H), 3.40 (s, 3H), 3.53 (t, 2H, J = 6.3 Hz), 3.62 (br, 1H), 3.74 (br, 1H), 3.79 (m, 2H), 3.96 (t, 1H, J = 4.2 Hz), 4.41 (ABq, Δδ = 0.20 ppm, 2H, J = 11.4 Hz), 4.47 (d, 1H, J = 6.3 Hz), 4.48 (ABq, Δδ = 0.24 ppm, 2H, J = 11.4 Hz), 4.65(ABq, Δδ = 0.13 ppm, 2H, J = 11.4 Hz), 4.74 (ABq, Δδ = 0.29 ppm, 2H, J = 11.4 Hz), 7.14 –7.34 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 26.39, 28.86, 54.79, 56.40, 63.04, 71.63, 73.02, 73.38, 74.21, 74.51, 75.95, 77.87, 78.36, 78.76, 106.00, 127.65 – 128.62 (several lines), 138.30, 138.44, 138.67, 138.81.

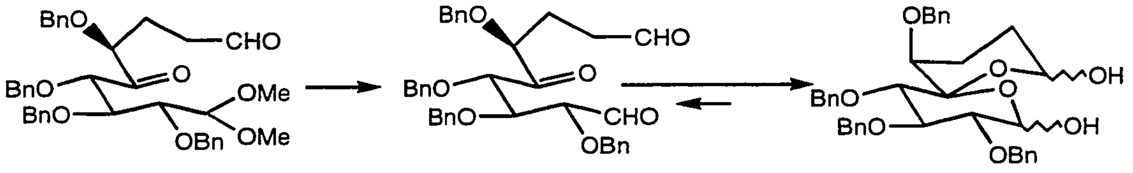
IV.5.2 Synthesis of Keto Aldehyde (IV-5)



(IV-4) **(IV-5)**

The standard Swern's oxidation procedure that was used for the preparation of **(II-8)** was applied to diol **(IV-4)** (1.04 g, 1.6 mmol). Keto aldehyde **(IV-5)** (0.92 g, 89%) was obtained. $R_f = 0.65$ (EtOAc : P.E = 30 : 70); $[\alpha]_D$ – 3.1 (c = 6.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.74 (m, 1H), 1.92 (m, 1H), 2.28 (m, 2H), 3.37 (s, 3H), 3.45 (s, 3H), 3.84 (dd, 1H, J = 3.9, 6.0 Hz), 4.14 (t, 1H J = 3.9 Hz), 4.15 (ABq, $\Delta\delta$ = 0.28 ppm, 2H, J = 12.0 Hz), 4.32 (m, 2H), 4.58 (d, 1H, J = 6.6 Hz), 4.63 (ABq, $\Delta\delta$ = 0.15 ppm, 2H, J = 11.4 Hz), 4.64 (s, 2H), 4.70 (ABq, $\Delta\delta$ = 0.16 ppm, 2H, J = 11.4 Hz), 7.12 – 7.40 (m, 20H), 9.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.57, 39.79, 54.52, 55.90, 71.91, 73.46, 74.26, 74.83, 77.66, 79.87, 80.42, 80.88, 105.55, 127.71 – 128.61 (several lines), 137.60, 137.97, 138.05, 138.81, 201.57, 201.69, 208.25.

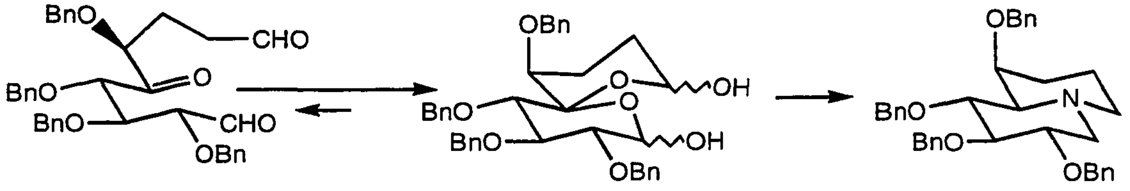
IV.5.3 Synthesis of Tricarbonyl Compound (IV-1)



(IV-5) **(IV-1a)** **(IV-1b)**

The keto-aldehyde **(IV-5)** (0.77g, 1.2 mmol) was subjected to the hydrolysis conditions that was used for the preparation of **(II-1)**. This procedure provided **(IV-1)** (0.55 g, 77 %). $[\alpha]_D$ +14.6 (c = 4.1, $CHCl_3$); R_f = 0.55 (EtOAc : P.E = 50 : 50); ^{1}H NMR ($CDCl_3$) δ 1.88 (br, 4H), 3.52 (t, 1H, J = 8.4 Hz), 3.74 (m, 1H), 3.90 (d, 1H, J = 9.3 Hz), 4.16 (m, 2H), 4.38 (m, 2H), 4.50 (m, 2H), 4.78 (m, 2H), 4.92 (d, 2H, J = 11.1 Hz), 5.01 (d, 2H, J = 11.1 Hz), 5.09 (br, 1H), 7.21 – 7.46 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 21.94, 31.54, 70.84, 73.23, 75.04, 75.37, 75.87, 78.33, 81.15, 84.21, 91.24, 92.88, 100.00, 127.70 – 128.32 (several lines), 137.99, 138.43, 138.54, 138.72.

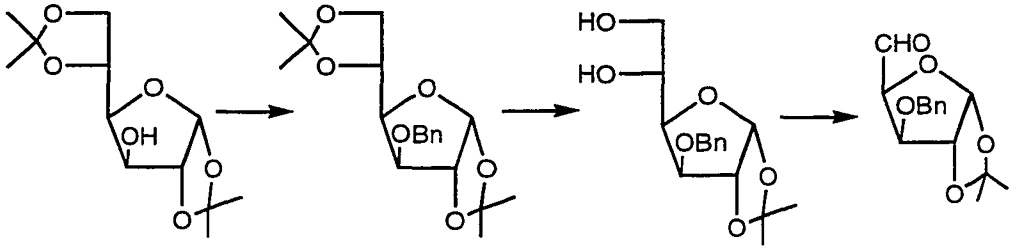
IV.5.4 Synthesis of 2,3,4,8 Tetra–O-benzyl Quinolizidine



(IV-1a) **(IV-1b)** **(IV-3)**

The standard TRA conditions was applied to **(IV-1)** (0.23 g, 0.39 mmol), using HCO_2NH_4 (0.041 g, 0.59 mmol), $NaCNBH_3$ (1.24 g, 11.7 mmol) and MeOH (20 mL). Compound **(IV-3)** (0.061 g, 30 %) was obtained. $R_f = 0.40$ (EtOAc : P.E = 30 : 70)); $[\alpha]_D$ +29.5 (c = 0.2, $CHCl_3$); ^1H NMR (C_6D_6) δ 0.91 (m, 1H), 1.13 (br, 1H), 1.91 (m, 5H), 2.70 (d, 1H, J = 10.8 Hz), 2.94 (dd, 1H, J = 4.5, 11.1 Hz), 3.64 (t, 2H, J = 9.0 Hz), 3.72 (m, 1H), 3.91 (br, 1H), 4.12 (t, 1H, J = 9.0 Hz), 4.22 (ABq, $\Delta\delta = 0.26$ ppm, 2H, J = 11.7 Hz), 4.49 (ABq, $\Delta\delta = 0.05$ ppm, 2H, J = 12.0 Hz), 4.87 (ABq, $\Delta\delta = 0.32$ ppm, 2H, J = 11.4 Hz), 5.03 (ABq, $\Delta\delta = 0.31$ ppm, 2H, J = 11.4 Hz), 7.03 – 7.38 (m, 20H); ^{13}C NMR (C_6D_6) δ 20.52, 26.74, 56.35, 59.74, 68.99, 70.76, 71.95, 73.09, 75.44, 75.83, 79.08, 79.18, 88.42, 127.58 – 128.86 (several lines), 139.86, 139.95, 140.23, 140.61.

IV.5.5 Synthesis of Furanoside Aldehyde (IV-9)



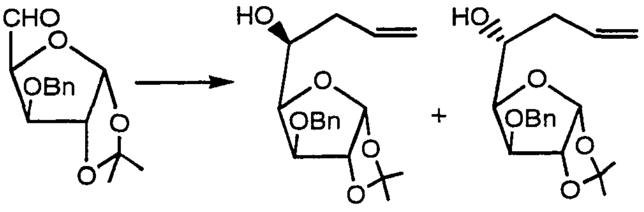
(IV-8) **(IV-8-1)** **(IV-8-2)** **(IV-9)**

1,2,5,6-Di-O-isoproylidiene glucofuranose **(IV-8)** (20 g, 77 mmol) was subjected to the standard benzylation procedure (section **II.4.2**). The crude benzyl ether **(IV-8-1)** was obtained. $R_f = 0.85$ (EtOAc : P.E = 30 : 70).

0.8% H_2SO_4 (100 mL) was added to a solution of the crude compound **(IV-8-1)** in methanol (100 mL). The mixture was stirred for 22 h at rt, then neutralized with saturated $NaHCO_3$, and extracted with ether (3 x 100 mL). The organic layer was dried (Na_2SO_4) and evaporated in *vacuo*. The residue was purified by flash column chromatography to afford compound **(IV-8-2)** (22.8 g, 95%) as a white solid. $R_f = 0.30$ (EtOAc : P.E = 30 : 70); ^{1}H NMR ($CHCl_3$) δ 1.30 (s, 3H), 1.47 (s, 3H), 2.83 (br, 2H), 3.67 (dd, 1H, J = 5.4, 11.4 Hz), 3.79 (dd, 1H, J = 3.3, 11.4 Hz), 4.02 (m, 1H), 4.09 (s, 1H), 4.11 (m, 1H), 4.60 (d, 1H, J = 3.6 Hz), 4.62 (ABq, $\Delta\delta$ = 0.13 ppm, 2H, J = 11.7 Hz), 5.91 (d, 1H, J = 3.6 Hz), 7.33 (m, 5H); ^{13}C NMR ($CHCl_3$) δ 26.34, 26.85, 64.46, 69.28, 72.32, 80.12, 82.09, 82.29, 105.27, 111.92, 127.94, 128.26, 128.77, 137.45.

To a solution of compound **(IV-8-2)** (22.7 g, 73.2 mmol) in methanol (200 mL) was added saturated aqueous $NaIO_4$ (18.8 g, 87.9 mmol) solution. The solution was stirred at rt for 30 min, then washed with saturated aqueous $Na_2S_2O_3$, extracted with ether (3 x), dried (Na_2SO_4), and evaporated in *vacuo*. The residue was purified by flash column chromatography to afford aldehyde **(IV-9)** (19.4 g, 69.5 mmol, 95 %). . tlc R_f = 0.60 (EtOAc : P.E = 30 : 70); ^{1}H NMR ($CHCl_3$) δ 1.32 (s, 3H), 1.47 (s, 3H), 4.12 (m, 1H), 4.28 (m, 1H), 4.60 (m, 3H), 6.03 (m, 1H), 7.32 (m, 5H), 9.67 (s, 1H); ^{13}C NMR ($CHCl_3$) δ 26.55, 27.16, 63.25, 72.47, 82.41, 84.79, 105.42, 112.36, 127.89, 128.73, 128.65, 136.83, 200.07.

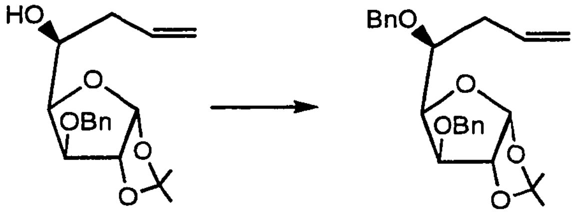
IV.5.6 Reaction of Aldehyde (IV-9) with Allyltrimethylsilane



(IV-9) **(IV-10)** **(IV-11)**

To a solution of compound **(IV-9)** (8.7 g, 31.1 mmol) in anhydrous CH_2Cl_2 (200 mL) at –78°C was added 1M $TiCl_4$ (47.0 mL, 47.0 mmol) solution. After the solution was stirred at –78°C for 10 min, allyl trimethylsilane (4.3 g, 37.3 mmol) was then added and the solution stirred at this temperature for additional 30 min, warmed up to rt, and neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted with ether (3 x 100 mL), and the organic layer dried (Na_2SO_4), filtered and evaporated in *vacuo*. The residue was purified by flash column chromatography to afford compounds **(IV-10)** (7.5 g, 75%) and **(IV-11)** (1.2 g, 12%) in a respective of ratio 6.5 : 1.[47]

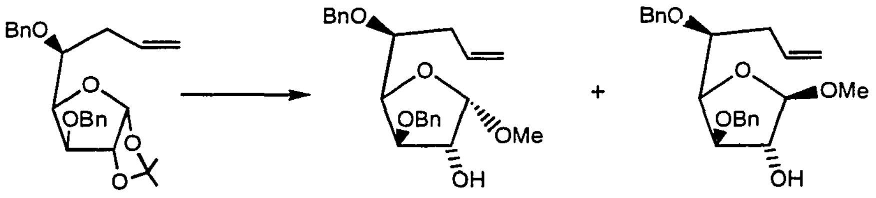
IV.5.7 Synthesis of Di-O-benzyl Ether (IV-12)



(IV-10) **(IV-12)**

Compound **(IV-10)** (7.5 g, 23 mmol) was subjected to the general benzylation procedure (section II.4.2) to afford **(IV-12)** (9.3 g, 97 %). tlc $R_f = 0.40$ (EtOAc : PE = 10 : 90); ^{1}H NMR ($CHCl_3$) δ 1.49 (s, 3H), 1.56 (s, 3H), 2.26 (m, 2H), 3.91(m, 1H), 3.97(d, 1H, J = 3.3 Hz), 4.30 (dd, 1H, J = 3.3, 8.1 Hz), 4.62 (ABq, Δδ = 0.26 ppm, 2H, J = 11.7 Hz), 4.70 (d, 1H, J = 3.9 Hz), 4.79 (ABq, Δδ = 0.27 ppm, 2H, J = 11.7 Hz), 5.04 (dd, 1H, J = 1.2, 19.5 Hz), 5.10 (d, 1H, J = 10.8 Hz), 6.00 (m,1H), 6.08 (d, 1H, J = 3.9 Hz), 7.21 – 7.46 (m, 10H); ^{13}C NMR ($CHCl_3$) δ 26.50, 26.88, 35.86, 71.59, 73.30, 77.73, 81.69, 82.12, 83.68, 105.12, 111.68, 116.94, 127.33 – 128.57 (several lines), 134.78, 137.103, 139.25.

IV.5.8 Synthesis of Furanoside Alkene Mixture (IV-13α/β)



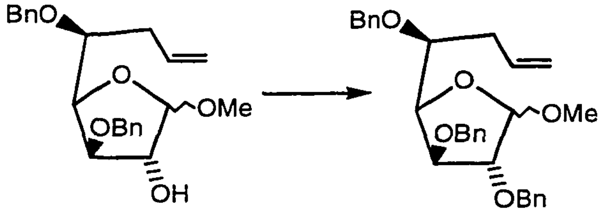
(IV-12) **(IV-13α)** **(IV-13β)**

HCl gas was bubbled through anhydrous methanol (20 mL) for 10 min. A portion of this solution (1.5 mL) was added to a solution of alkene **(IV-12)** (1.21 g, 2.9 mmol) in anhydrous methanol (15 mL) for 30 min. Solid $NaHCO_3$ was carefully added to the reaction mixture until the solution was neutral. Concentration of the reaction mixture under reduced pressure, followed by flash chromatography of the residual slurry afforded a less polar product, **(IV-13β)** (0.58 g, 51 %) and a more polar product, **(IV-13α)** (0.49 g, 43 %). The α/β conformation of acetal was assigned by ^{13}C NMR[51]. The chemical shift of the acetal carbon in **(IV-13α)** is more downfield than that in **(IV-13β)**.

For **(IV-13β)** $R_f = 0.40$ (EtOAc : PE = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.25 (m, 2H), 2.85 (d, 1H, J = 6.9 Hz), 3.40 (s, 3H), 3.67 (dd, 1H, J = 6.0, 12.0 Hz), 3.86 (dd, 1H, J = 3.3, 5.4 Hz), 4.07 (t, 1H, J = 6.0 Hz), 4.29 (m, 1H), 4.56 (ABq, Δδ = 0.23 ppm, 2H, J = 11.7 Hz), 4.61 (ABq, Δδ = 0.21 ppm, 2H, J = 11.7 Hz), 4.95 (m, 3H), 5.79 (m, 1H), 7.26 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 35.96, 55.78, 71.78, 73.02, 76.80, 77.64, 80.69, 83.84, 101.65, 117.13, 127.34, 127.86, 127.99, 128.19, 128.42, 134.84, 137.69, 139.05;

For **(IV-13α)** $R_f = 0.30$ (EtOAc : PE = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.29 (m, 1H), 2.34 (m, 1H), 2.80 (d, 1H, J = 3.3 Hz), 3.48 (s, 3H), 3.77 (dd, 1H, J = 4.8, 1.5 Hz), 3.90 (m, 1H), 4.22 (dd, 1H, J = 4.5, 8.4 Hz), 4.24 (s, 1H), 4.54 (ABq, Δδ = 0.29 ppm, 2H, J = 11.7 Hz), 4.76 (ABq, Δδ = 0.28 ppm, 2H, J = 11.4 Hz), 4.88 (s, 1H), 5.02 (m, 2H), 5.93 (m, 1H), 7.36 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 35.80, 56.13, 71.68, 73.39, 77.89, 78.76, 82.38, 84.03, 110.13, 116.99, 127.45, 127.91, 128.00, 128.28, 128.34, 128.47, 134.75, 137.39, 139.05.

IV.5.9 Synthesis of 2,3,5-Tri-O-benzyl Furanoside (IV-14α/β)



(IV-13α/β) **(IV-14α/β)**

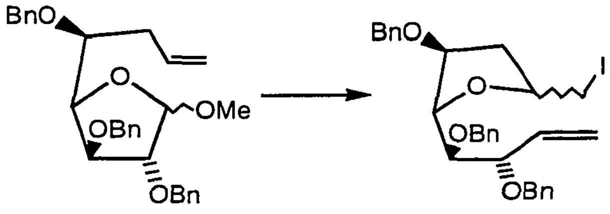
The general benzylation procedure (section **II.4.2**) was applied to the separated samples of **(IV-13β)** (0.42 g, 1.1 mmol), **(IV-13α)** (0.46 g, 1.2 mmol) and a mixture of **(IV-13α/β)** (7.5 g, 25.0 mmol). Compound **(IV-14β)** (0.36 g, 69 %), **(IV-14α)** (0.48 g, 85 %) and a mixture of **(IV-14α/β)** were obtained respectively.

For **(IV-14β)**; R_f = 0.50 (EtOAc : PE = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.33 (t, 2H, J = 6.6 Hz), 3.39 (s, 3H), 3.64 (m, 1H), 4.15 (m, 2H), 4.25 (t, 1H, J = 6.3 Hz), 4.55 (ABq, Δδ = 0.12 ppm, 2H, J = 11.4 Hz), 4.58 (ABq, Δδ = 0.17 ppm, 2H, J = 12.3 Hz), 4.68 (ABq, Δδ = 0.16 ppm, 2H, J = 11.7 Hz), 4.82 (d, 1H, J = 4.2 Hz), 5.00 (s, 1H), 5.05 (d, 1H, J = 6.0 Hz), 5.80 (m, 1H), 7.30 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 36.21, 55.42, 72.71, 72.84, 72.93, 77.45, 78.38, 81.85 83.34, 100.71, 117.29, 127.41, 127.81, 127.99, 128.22, 128.28, 128.47, 135.07, 137.93, 138.14, 139.02.

For **(IV-14α)**; R_f = 0.45 (EtOAc : PE = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.23 (m, 1H), 2.33 (m, 1H), 3.52 (s, 3H), 3.91 (m, 2H), 4.07 (s, 1H), 4.21 (dd, 1H, J = 4.5, 8.1 Hz), 4.51 (ABq, Δδ = 0.28 ppm, 2H, J = 12.0 Hz), 4.61 (ABq, Δδ = 0.09 ppm, 2H, J = 12.3 Hz), 4.78 (ABq, Δδ = 0.21 ppm, 2H, J = 11.4 Hz), 5.03 (m, 3H), 5.93 (m, 1H), 7.38 (m, 15H);

^{13}C NMR ($CDCl_3$) δ 35.90, 56.30, 71.59, 72.05, 73.43, 78.55, 80.67, 84.25, 85.23, 108.63, 116.85, 127.33, 127.82, 128.03, 128.08, 128.25, 128.48, 128.59, 134.94, 137.31, 137.61, 139.33

IV.5.10 Synthesis of Iodo THF's Alkene (IV-7)

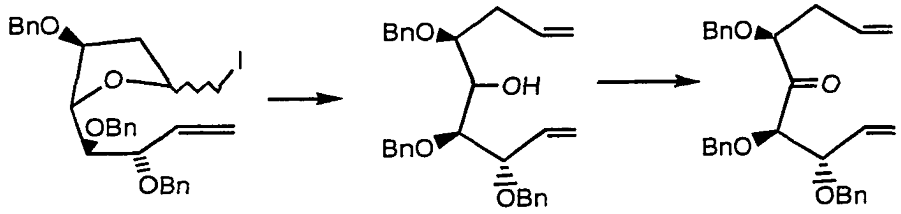


(IV-14α/β) **(IV-7)**

The mixture **(IV-14α/β)** from last step was treated according to the general iodoetherification procedure. A mixture iodo-THF's aldehyde (9.7 g, 82 % from a mixture of **(IV-13α/β)**) was obtained. R_f = 0.60 (EtOAc : PE = 20 : 80); ^1H NMR ($CDCl_3$) δ 1.62 (m, 1H), 2.33 (m, 1H), 3.26 (m, 2H), 3.75 (br, 1H), 3.83 (m, 1H), 4.05 (m, 1H), 4.20 (dd, 1H, J = 4.2, 7.2 Hz), 4.24 (m, 2H), 4.43 (m, 2H), 4.58 (m, 1H), 4.67 (m, 1H), 4.81 (m, 1H), 7.29 (m, 15H), 9.62 (s, 1H), 9.64 (s, 1H).

The mixture of aldehyde (1.0 g, 1.7 mmol) from previous step was subjected to the standard Wittg methylenation procedure using CH_3Ph_3PI (2.1 g, 5.1 mmol) and 1 M $NaN(SiMe_3)_2$ (4.8 mL, 4.8 mmol) in hexane **(II-24)** (Scheme II-8). Flash chromatography of the crude reaction mixture provided alkene **(IV-7)** (0.94 g, 94 %). R_f = 0.60 (EtOAc : PE = 20 : 80); ^1H NMR ($CDCl_3$) δ 1.67 (m, 1H), 2.39 (m, 1H), 3.37 (m, 2H), 3.76 (br, 1H), 3.85 (m, 1H), 3.99 (m, 2H), 4.22 (m, 1H), 4.43 (m, 3H), 4.70 (m, 2H), 4.97 (m, 1H), 5.31 (m, 2H), 6.08 (m, 1H), 7.37 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 11.64, 37.92, 69.88, 70.98, 74.63, 74.73, 77.13, 79.68, 81.24, 83.38, 118.54, 127.16, 127.24, 127.67, 127.81, 127.87, 127.99, 128.19, 128.28, 128.34, 128.63, 128.73, 136.25, 137.80, 138.24, 139.21.

IV.5.10 Synthesis of Keto Diene (IV-15)



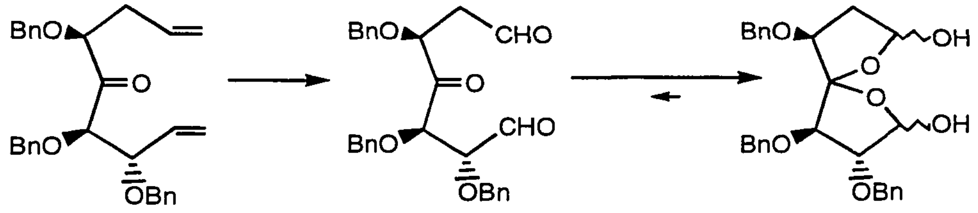
(IV-7) **(IV-7-1)** **(IV-15)**

The general reductive elimination procedure (section II.4.4) was applied to a mixture of **(IV-7)** (0.60 g, 1.0 mmol) to give **(IV-7-1)** (0.40 g, 85 %). $R_f = 0.65$ (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.22 (m, 1H), 2.45 (m, 1H), 2.64 (d, 1H, J = 4.8 Hz), 3.59 (dd, 1H, J = 5.1, 11.4 Hz), 3.67 (dd, 1H, J = 3.6, 6.0 Hz), 3.86 (dd, 1H, J = 4.8, 6.0 Hz), 4.17 (t, 1H, J = 6.9 Hz), 4.55 (ABq, Δδ = 0.25 ppm, 2H, J = 11.4 Hz), 4.57 (ABq, Δδ = 0.23 ppm, 2H, J = 11.4 Hz), 4.85 (ABq, Δδ = 0.25 ppm, 2H, J = 11.4 Hz), 5.13 (m, 2H), 5.40 (m, 2H), 5.92 (m, 2H), 7.38 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 34.44, 70.66, 71.61, 72.07, 74.50, 78.76, 80.16, 81.69, 117.48, 119.20, 127.65, 127.77, 128.10, 128.34, 128.41, 134.36, 135.33, 138.34, 138.51.

Compound **(IV-7-1)** (0.40 g, 0.87 mmol) was subjected to the standard Swern's oxidation procedure (section II.4.5). **(IV-15)** (0.35 g, 88 %) was obtained. $R_f = 0.75$ (EtOAc : P.E = 20 : 80); ^{1}H NMR ($CDCl_3$) δ 2.55 (m, 2H), 4.08 (t, 1H, J = 5.4 Hz), 4.32

(ABq, Δδ = 0.15 ppm, 2H, J = 11.4 Hz), 4.37 (d, 1H, J = 7.8 Hz), 4.42 (d, 1H, J = 3.9 Hz), 4.51 (ABq, Δδ = 0.34 ppm, 2H, J = 12.0 Hz), 4.65 (ABq, Δδ = 0.20 ppm, 2H, J = 11.7 Hz), 5.13 (m, 2H), 5.36 (m, 2H), 5.80 (m, 1H), 5.96 (m, 1H), 7.35 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 34.81, 70.34, 71.93, 73.74, 79.96, 81.88, 84.34, 117.94, 119.57, 127.78, 128.39, 128.35, 128.39, 133.50, 134.63, 137.61, 137.69, 137.90, 207.46.

IV.5.11 Synthesis of Tricarbonyl Compound (IV-6)

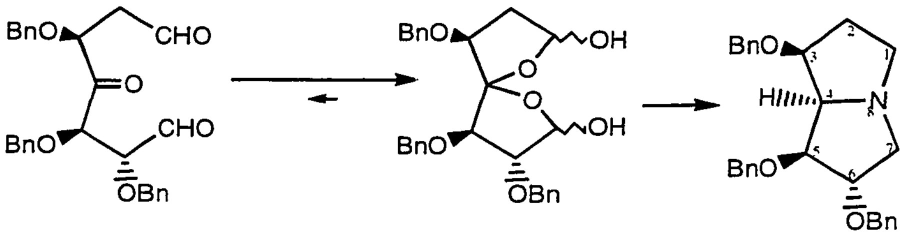


(IV-15) **(IV-6a)** **(IV-6b)**

O_3 was bubbled at -78 °C, through a solution of keto-diene **(IV-15)** (0.50 g, 1.1 mmol) in CH_2Cl_2 (10 mL). The progress of the reaction was monitored by tlc until complete disappearance of the starting material. The reaction vessel was purged with argon, and the reaction mixture warmed to rt. Ph_3P (0.54 g, 2.1 mmol) was then added and stirring continued under an argon atmosphere for 1h. Concentration of the reaction mixture under reduced pressure, followed by flash chromatography of the residual slurry afforded the keto-dialdehyde **(IV-6)** (0.28 g, 53 %) and some dicarbonyl compounds (0.13 g, 25 %). **(IV-6)** R_f = 0.35 (EtOAc : P.E = 50 : 50); ^{1}H NMR ($CDCl_3$) δ 1.34, 1.96, 2.20, 2.47 (all m, 4H), 4.01 (m, 1H), 4.18 (m, 1H), 4.37 (m, 1H), 4.53 – 4.84 (m, 6H), 5.22 – 5.75 (m, 2H), 7.28 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 38.45, 38.62, 60.53, 72.07 –

73.32 (several lines), 74.89, 75.53, 81.81, 83.83, 87.35, 93.93, 97.68, 99.67, 110.57, 111.88, 127.54 – 128.65 (several lines), 135.59, 137.30, 137.36, 137.40, 137.56, 137.60, 137.67, 137.72, 137.82, 138.10.

IV.5.12 Synthesis of Tri-O-benzyl Pyrrolizidine (IV-16)

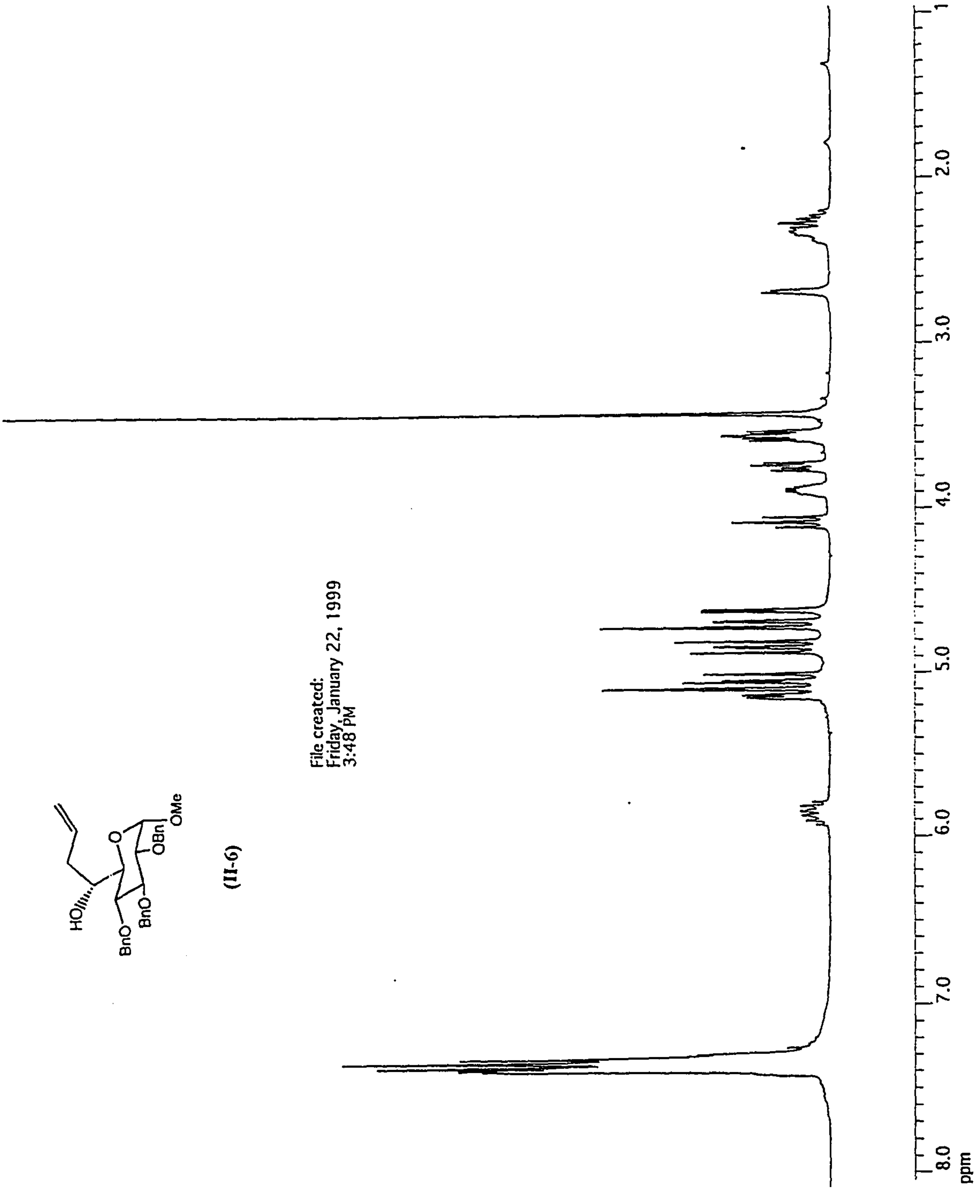


(IV-6a) **(IV-6b)** **(IV-16)**

The standard TRA procedure was applied to **(IV-6)** (0.060 g, 0.13 mmol). **(IV-16)** (0.012 g, 21 %) was obtained. $R_f = 0.30$ (EtOAc : P.E = 30 : 70); ^{1}H NMR (C_6D_6) δ 1.35 (m, 1H), 1.83 (m, 1H), 2.71 (m, 1H), 2.75 (dd, 1H, J = 3.2, 12.8 Hz), 3.41 (m, 1H), 3.48 (dd, 1H, J = 4.8, 12.8 Hz), 3.61 (br, 1H), 3.66 (m, 1H), 3.84 (m, 1H), 3.85 (s, 2H), 3.92 (m, 1H), 4.09 (ABq, $\Delta\delta = 0.10$ ppm, 2H, J = 12.4 Hz), 4.28 (ABq, $\Delta\delta = 0.11$ ppm, 2H, J = 12.0 Hz), 7.15 (m, 15H); ^{13}C NMR (C_6D_6) δ 30.71, 62.13, 64.85, 66.33, 71.62, 72.32, 80.28, 81.29, 83.42, 83.86, 128.06, 128.39, 128.49, 128.71, 129.02, 129.07, 129.12, 138.07, 138.42.

Appendix

^{1}H, ^{13}C and 2D NMR data of important compounds



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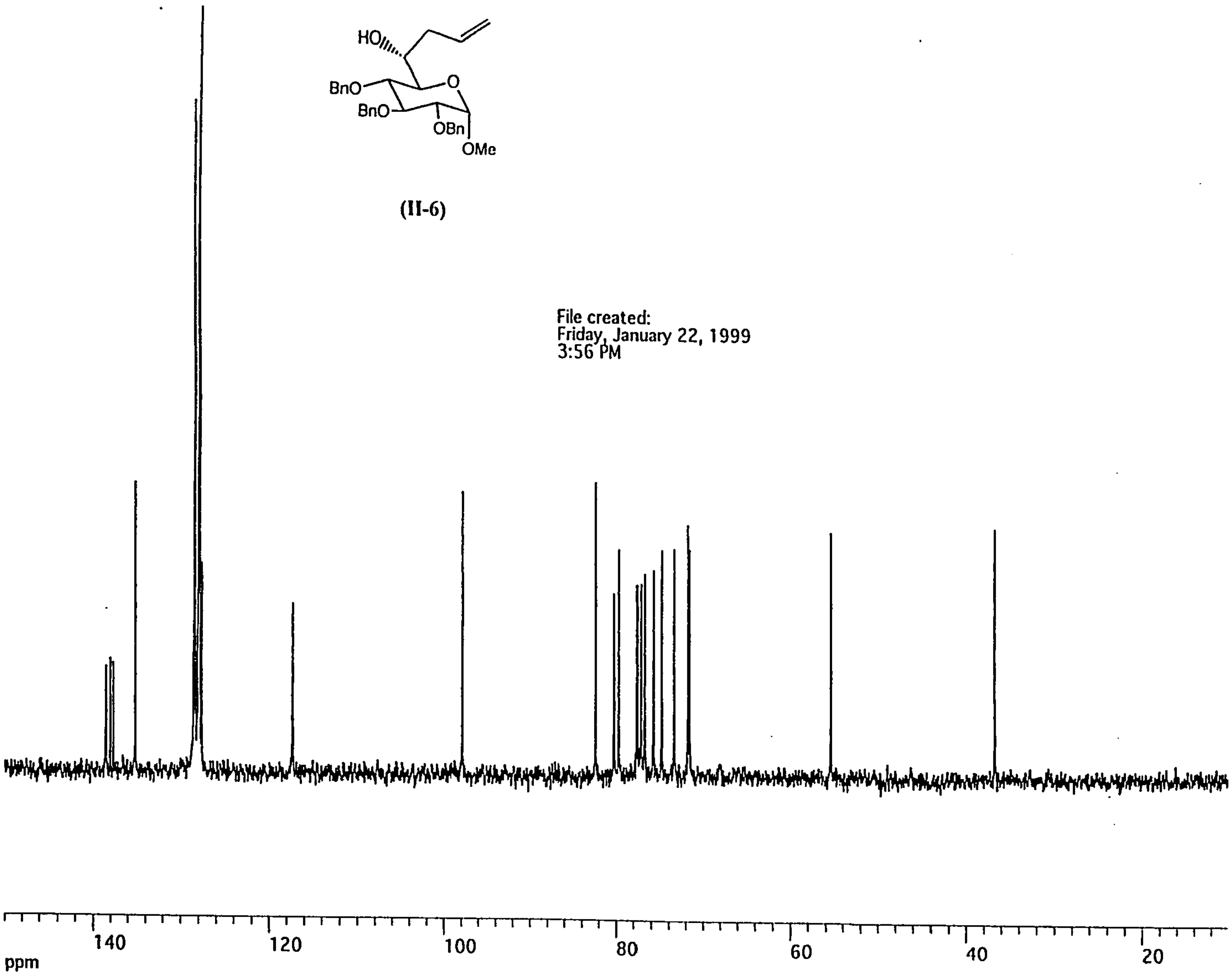

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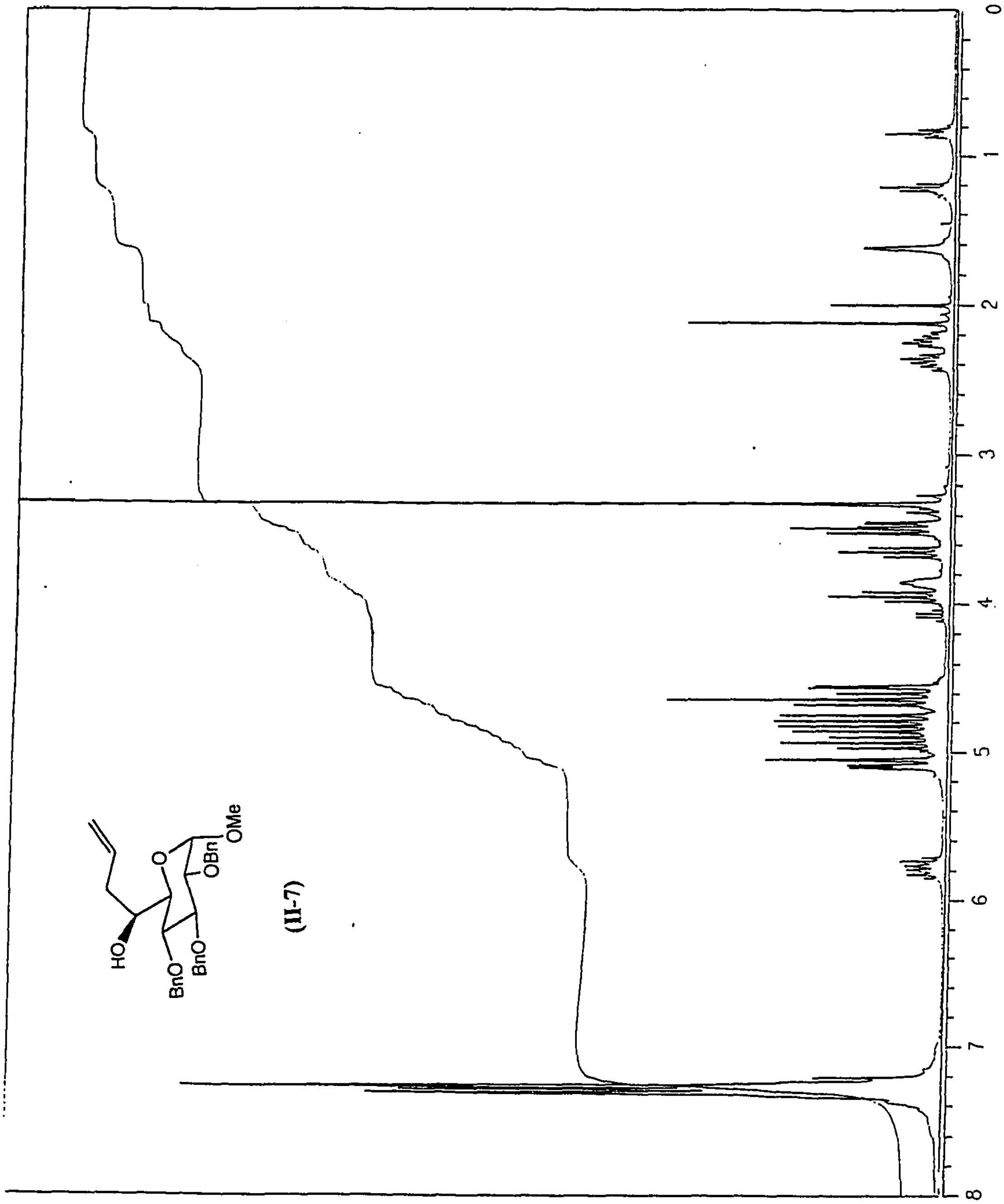

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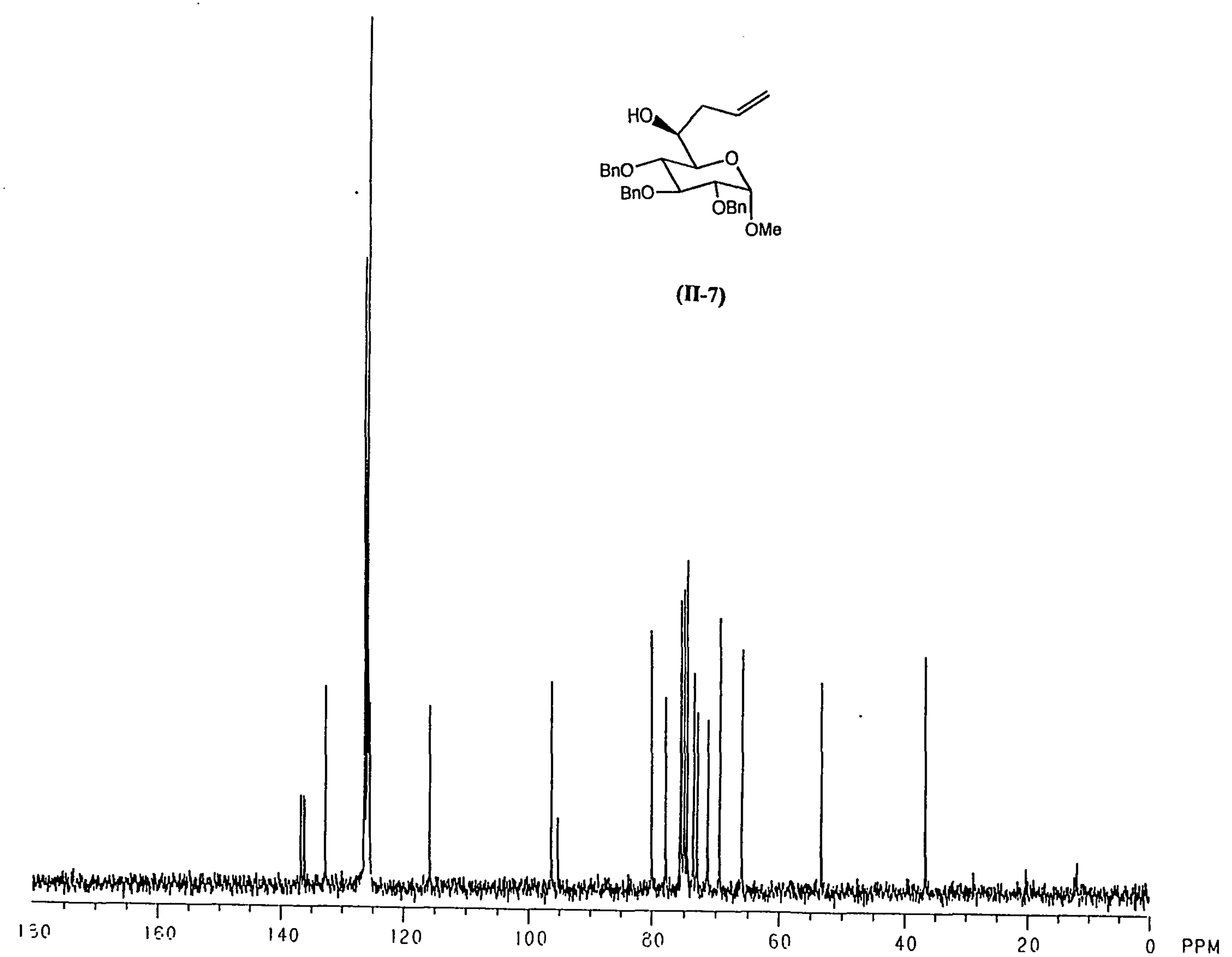

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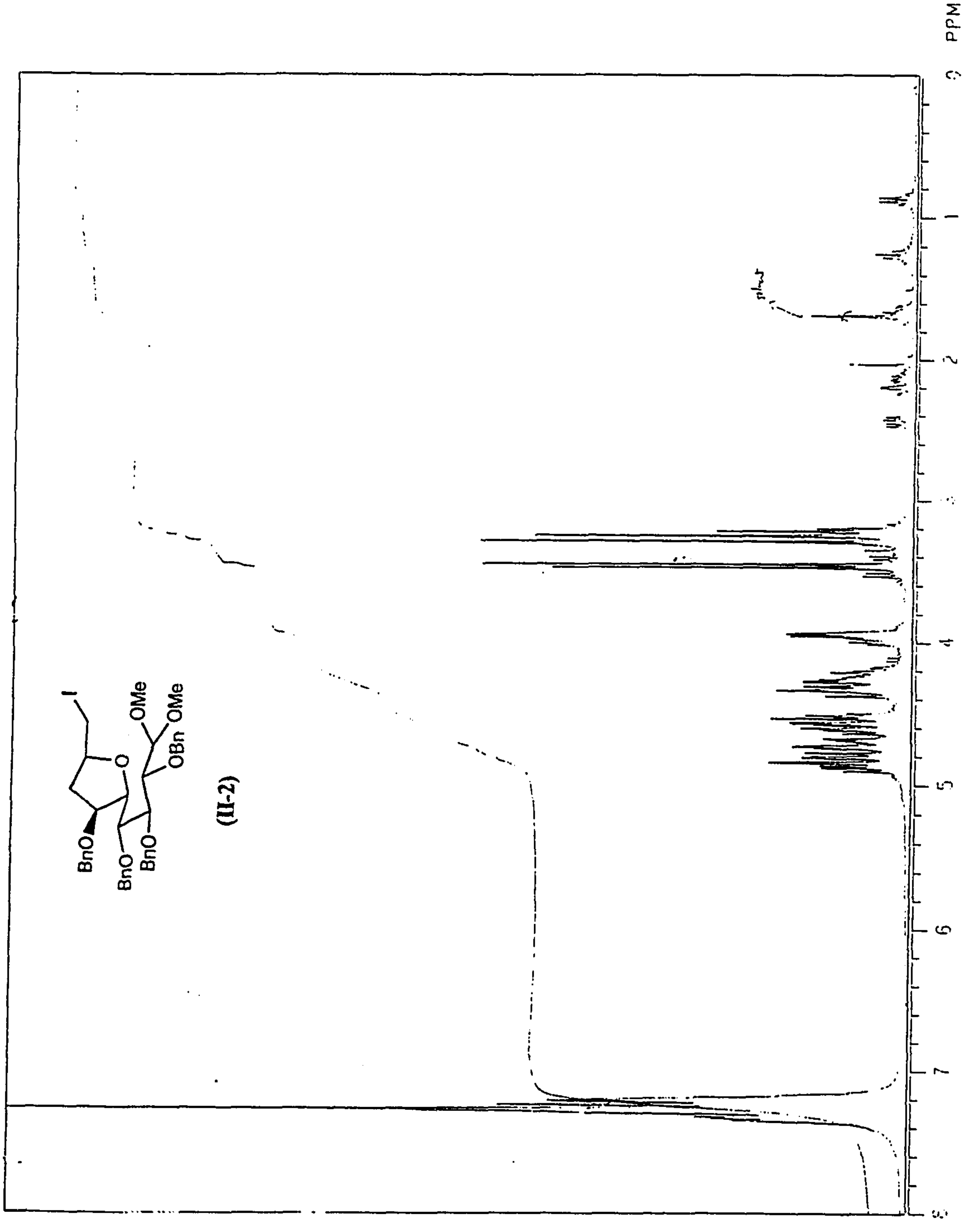

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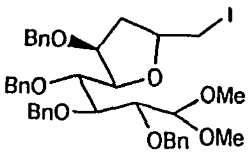

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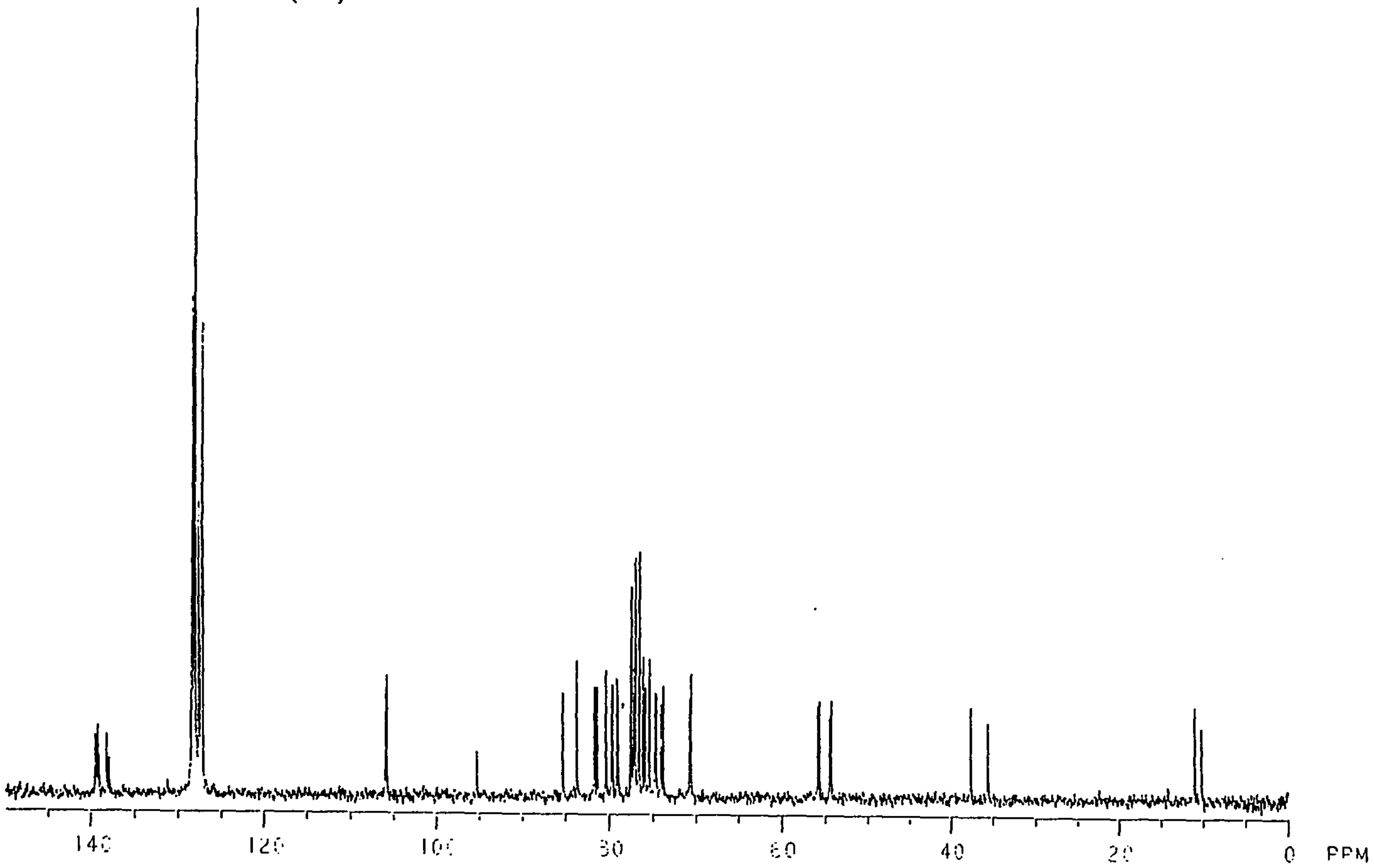

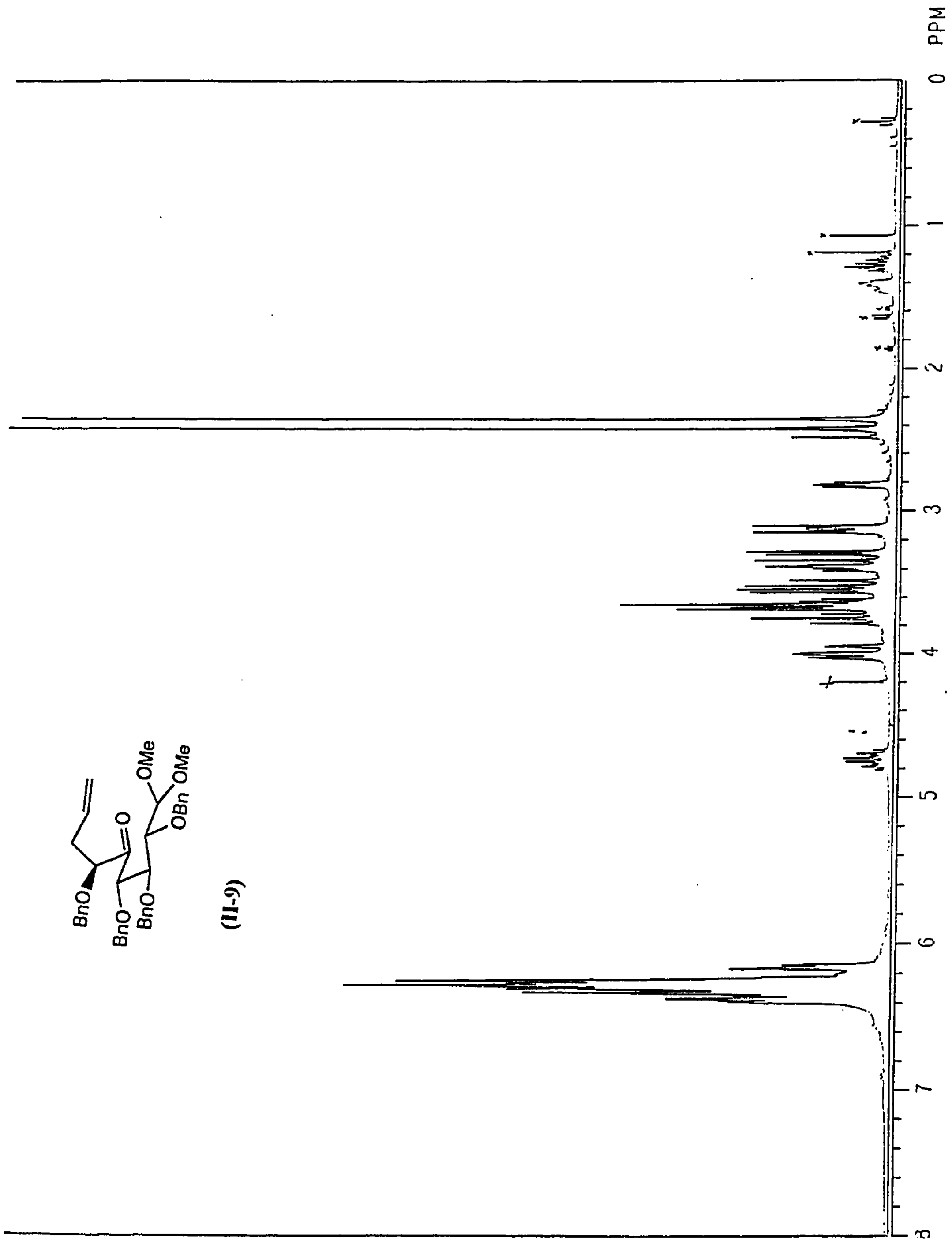

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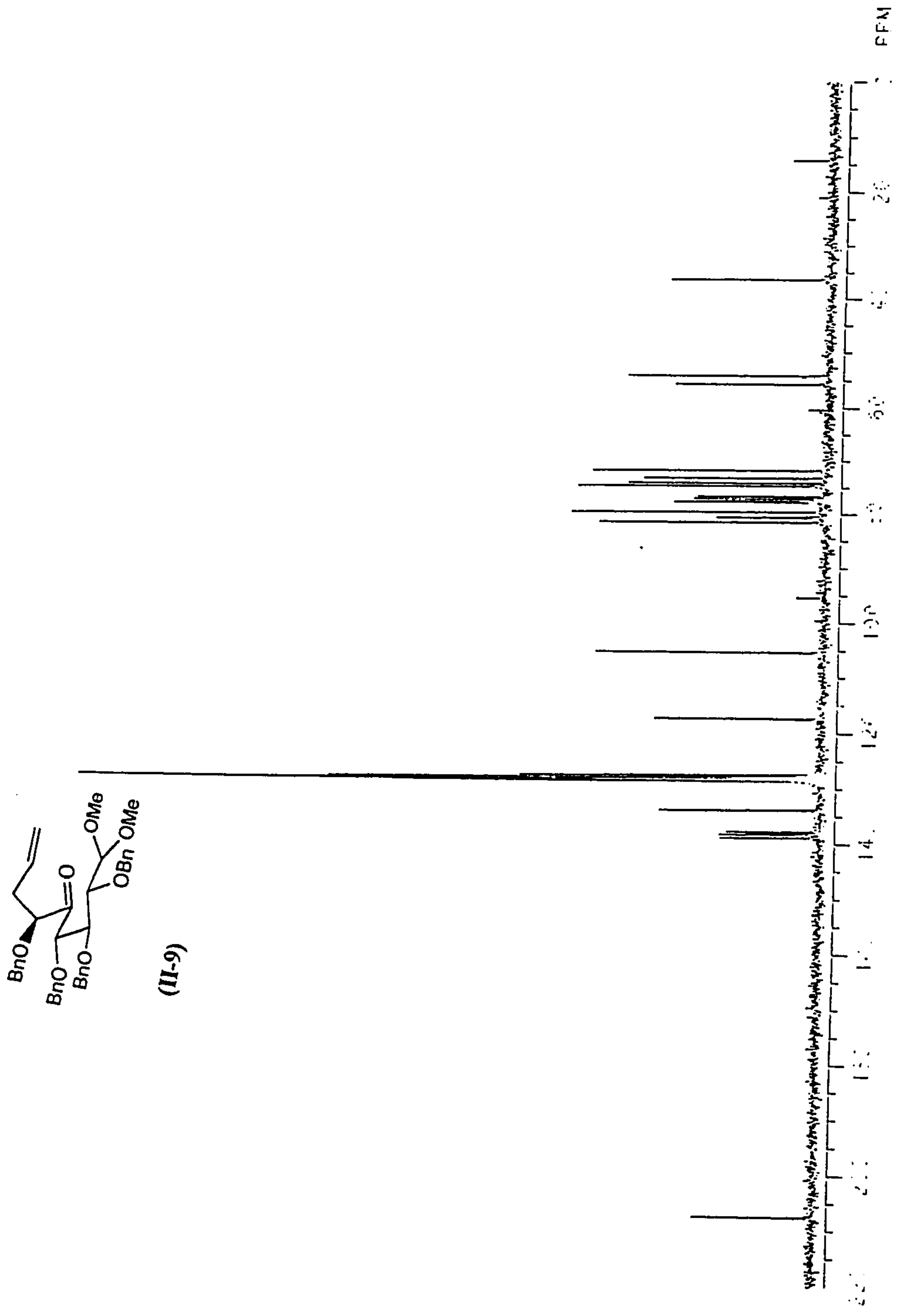

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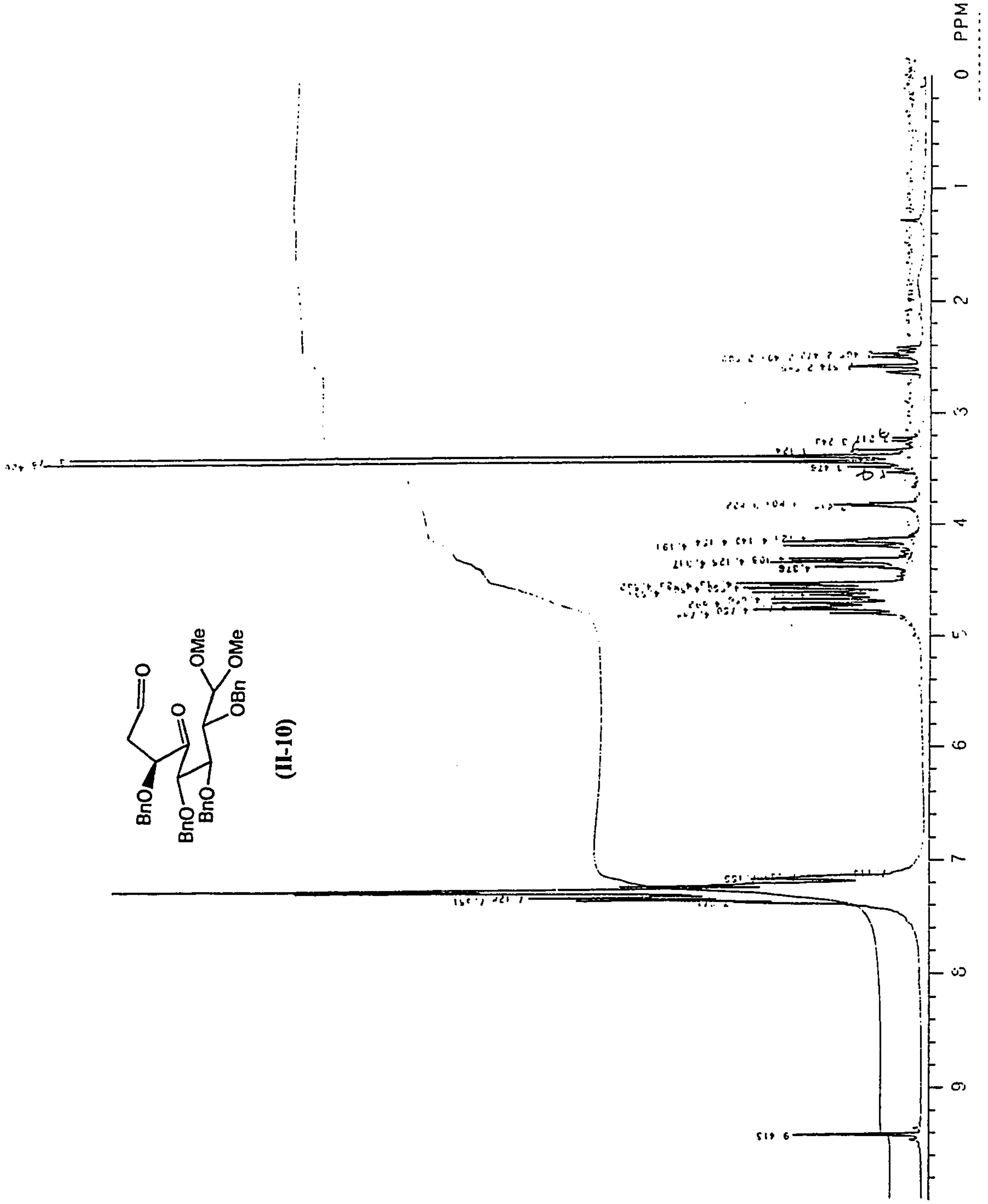

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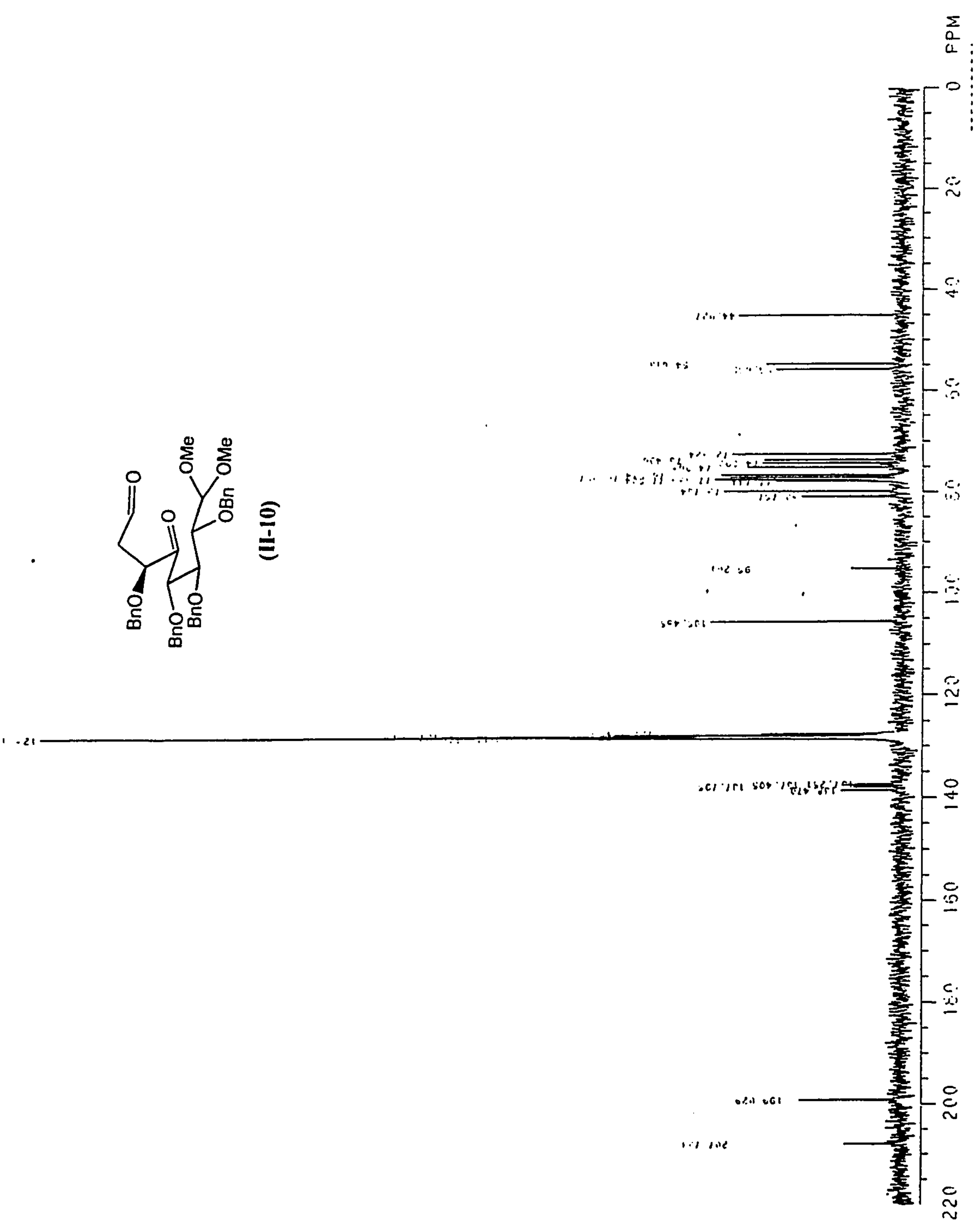
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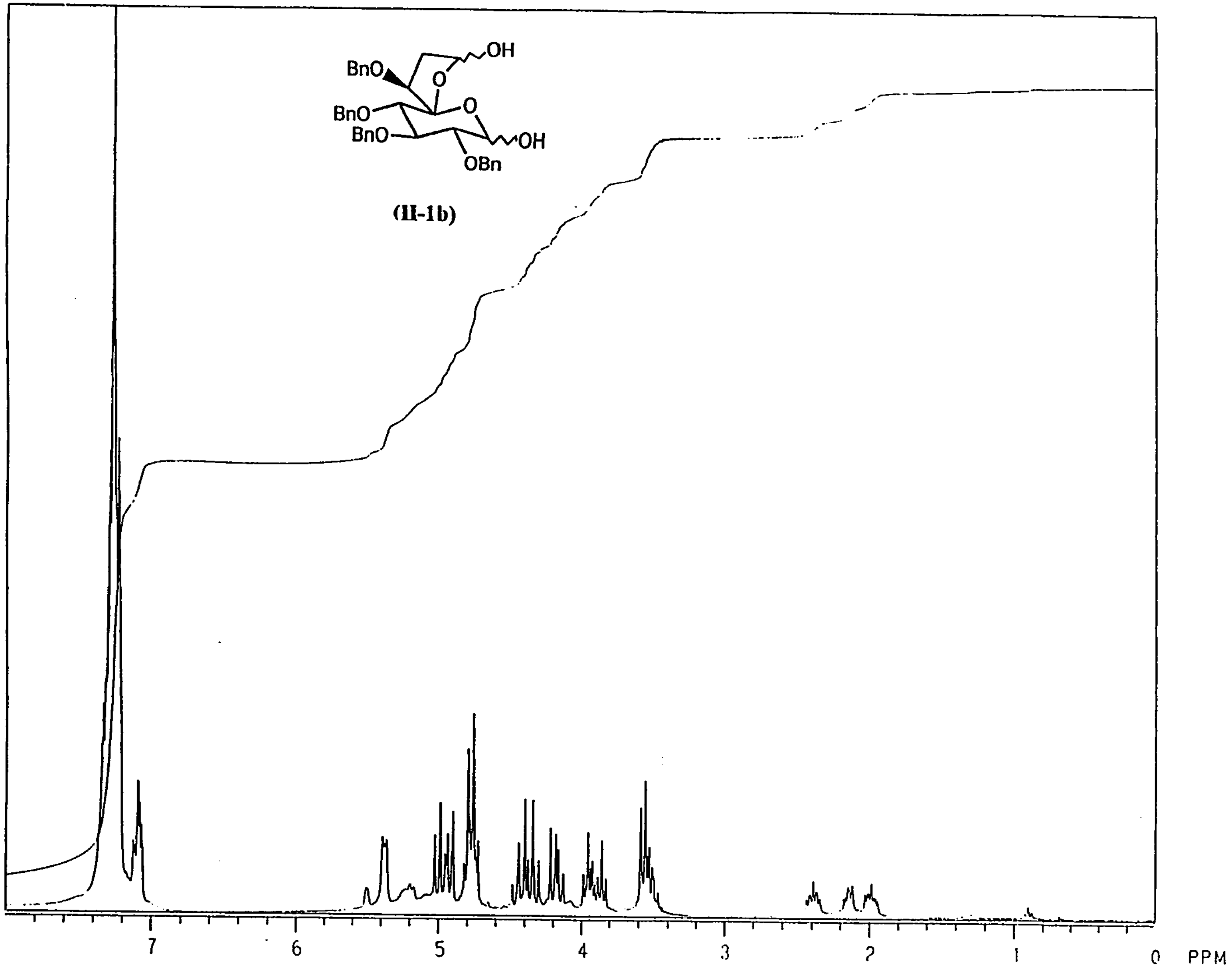

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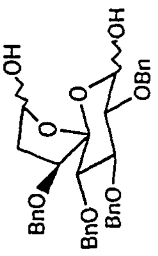

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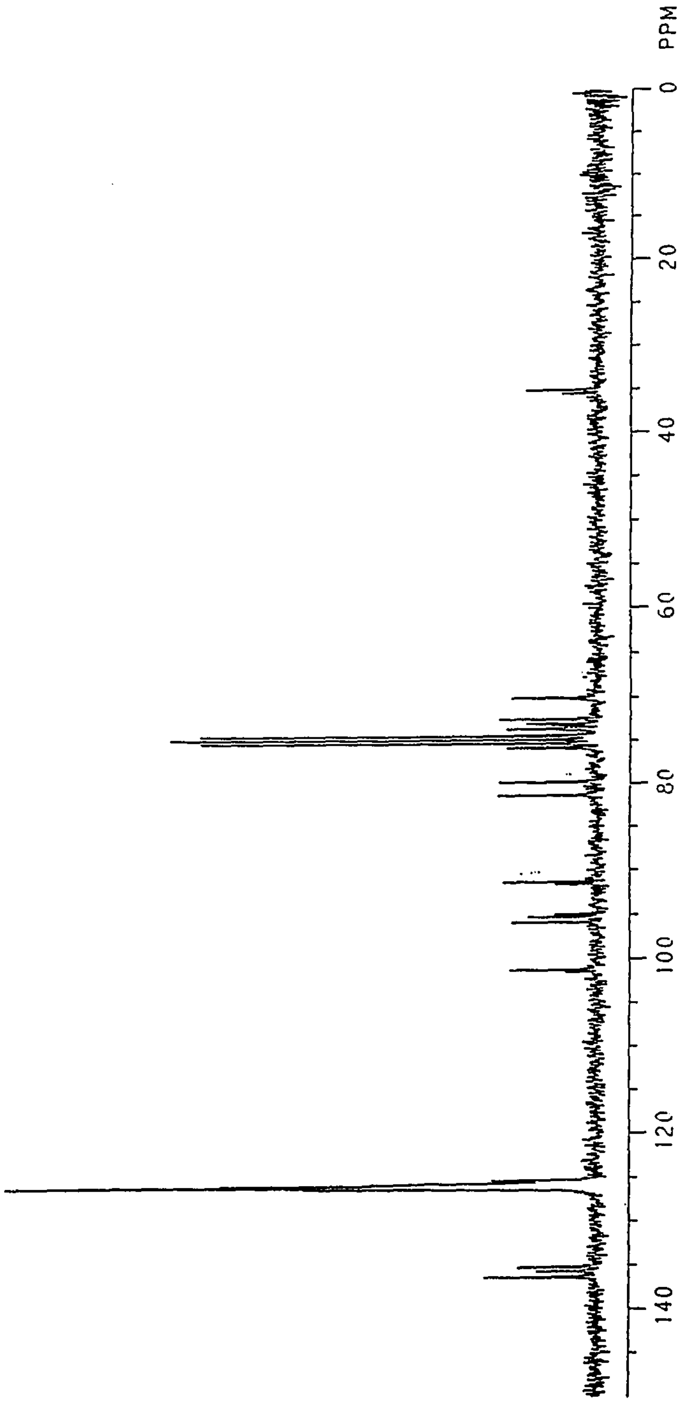

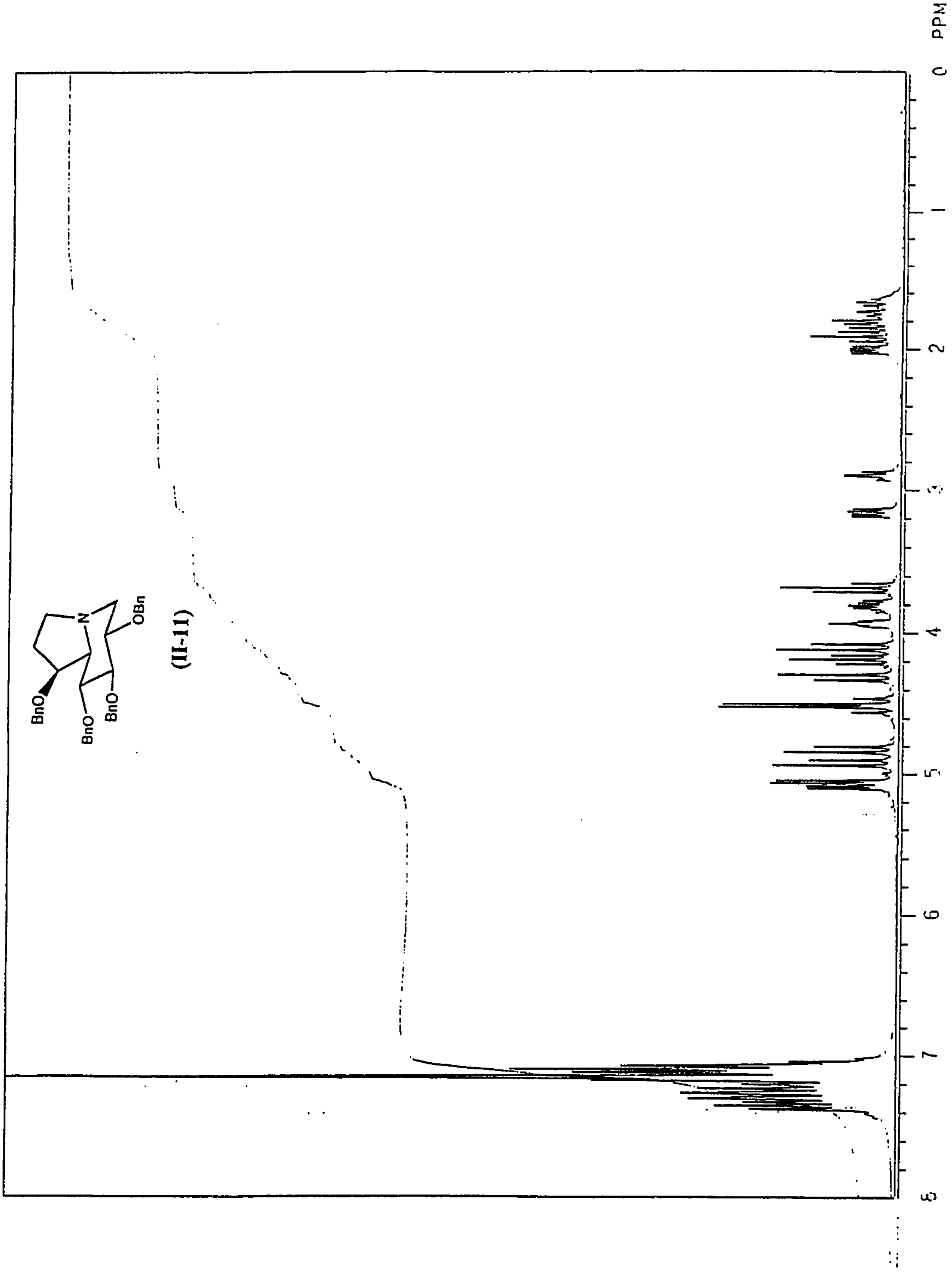

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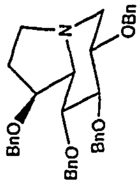

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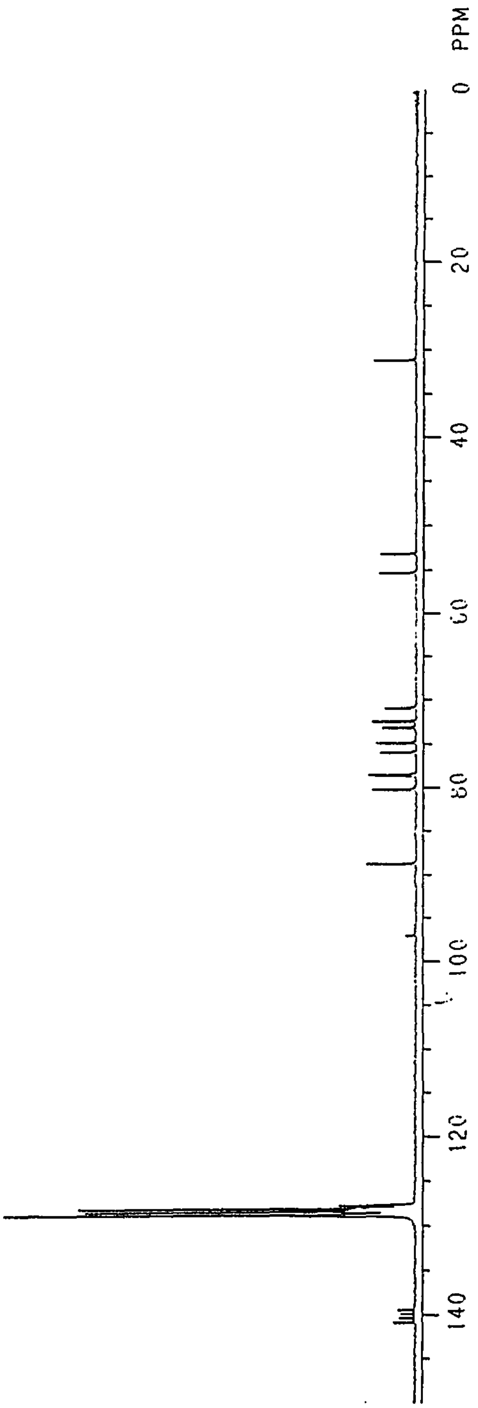

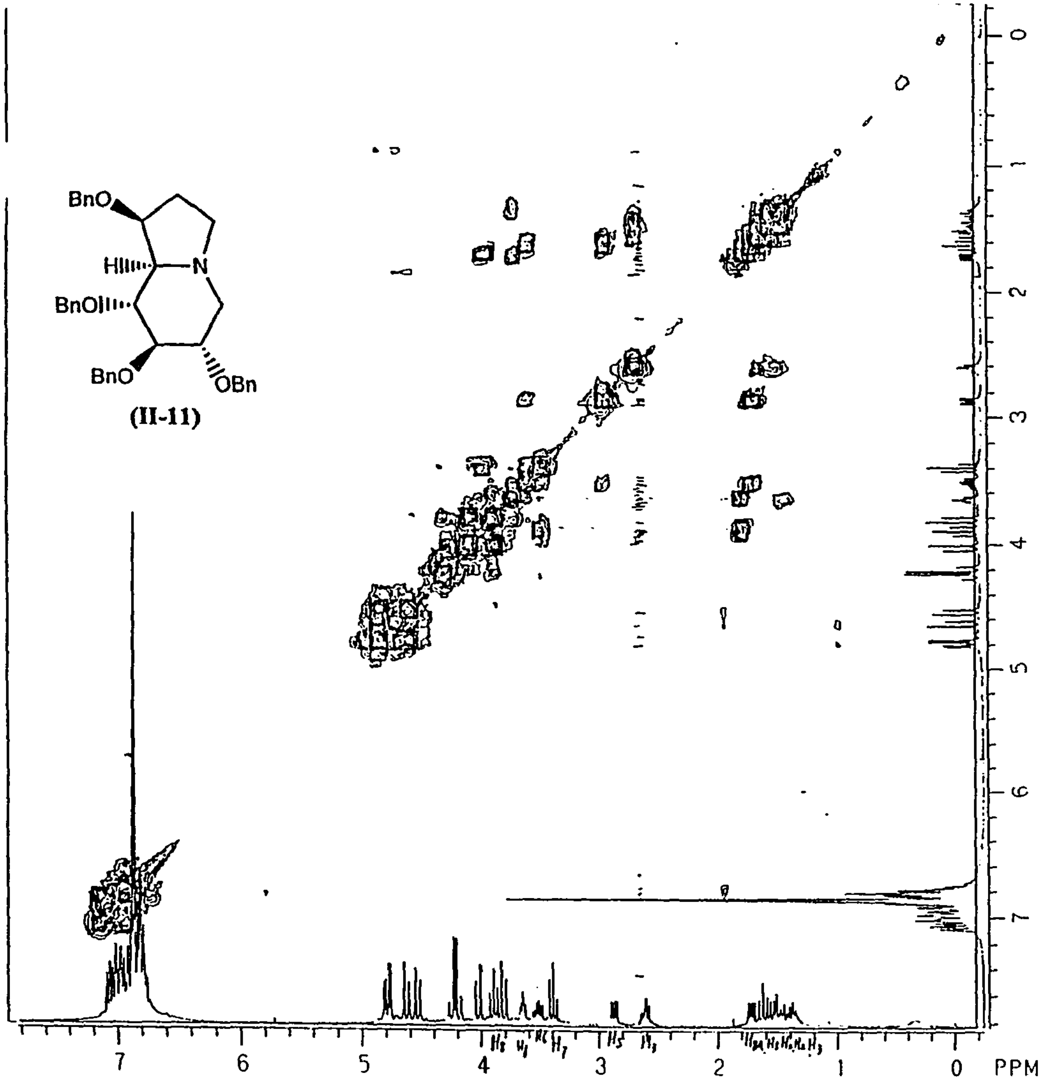

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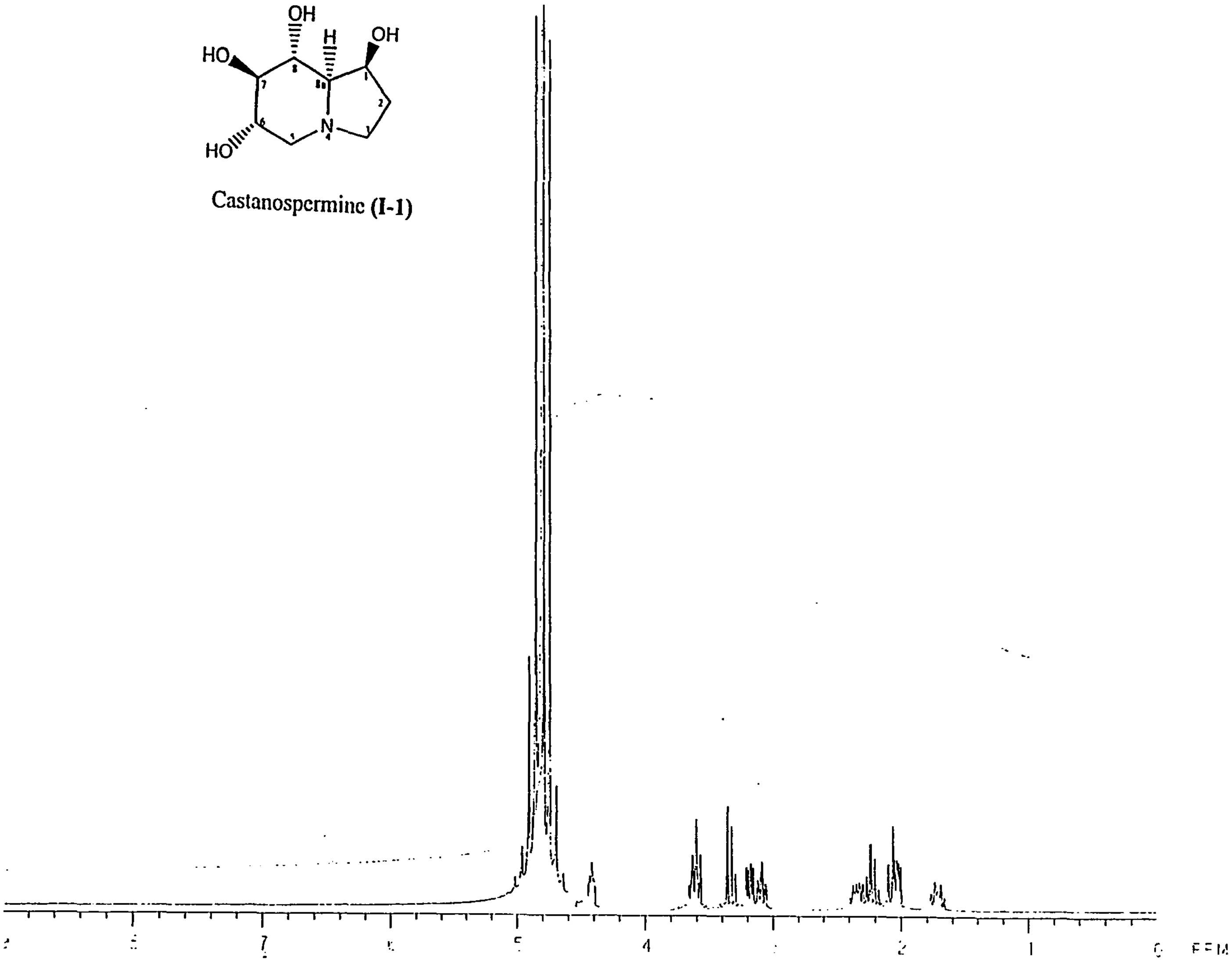

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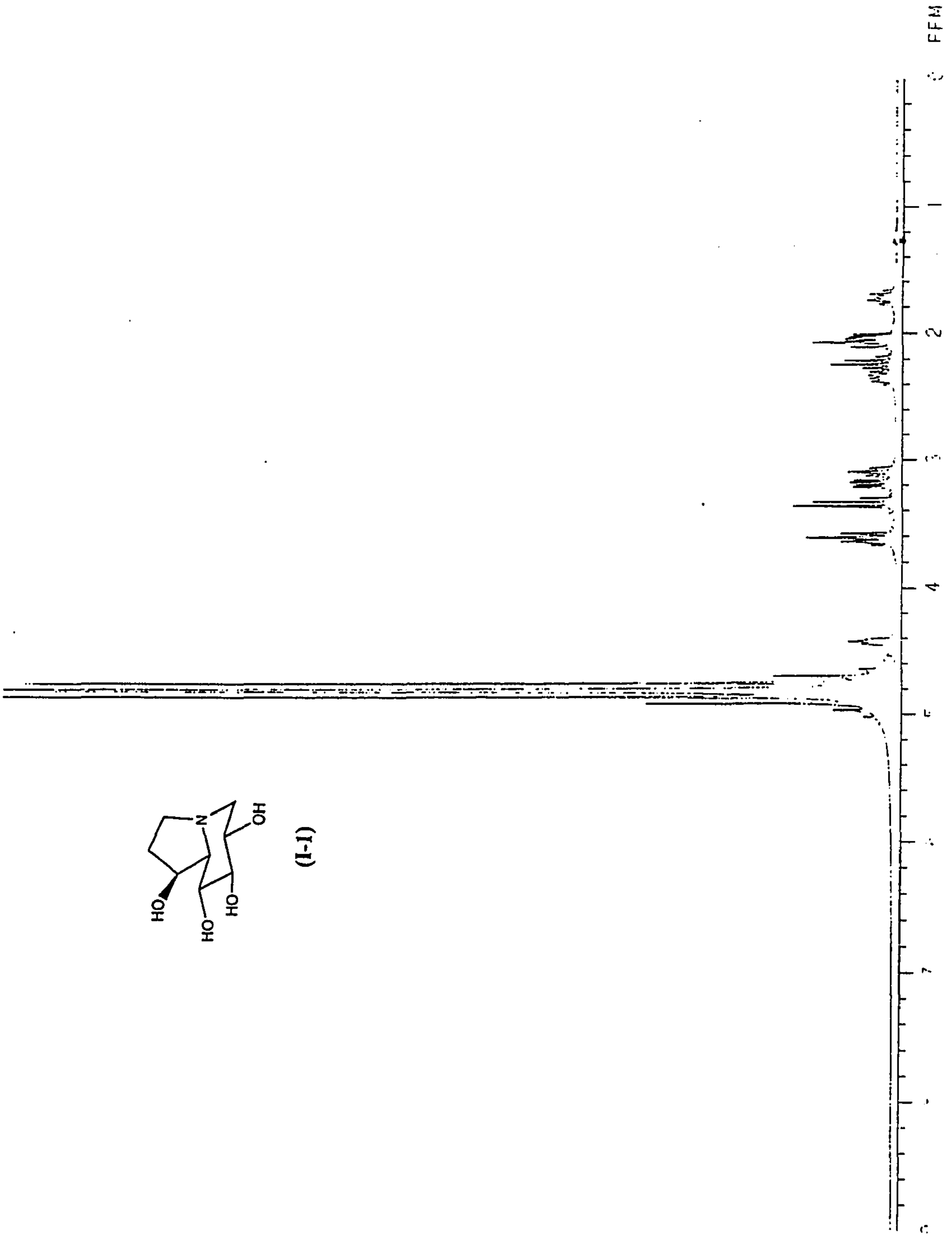

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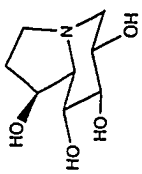

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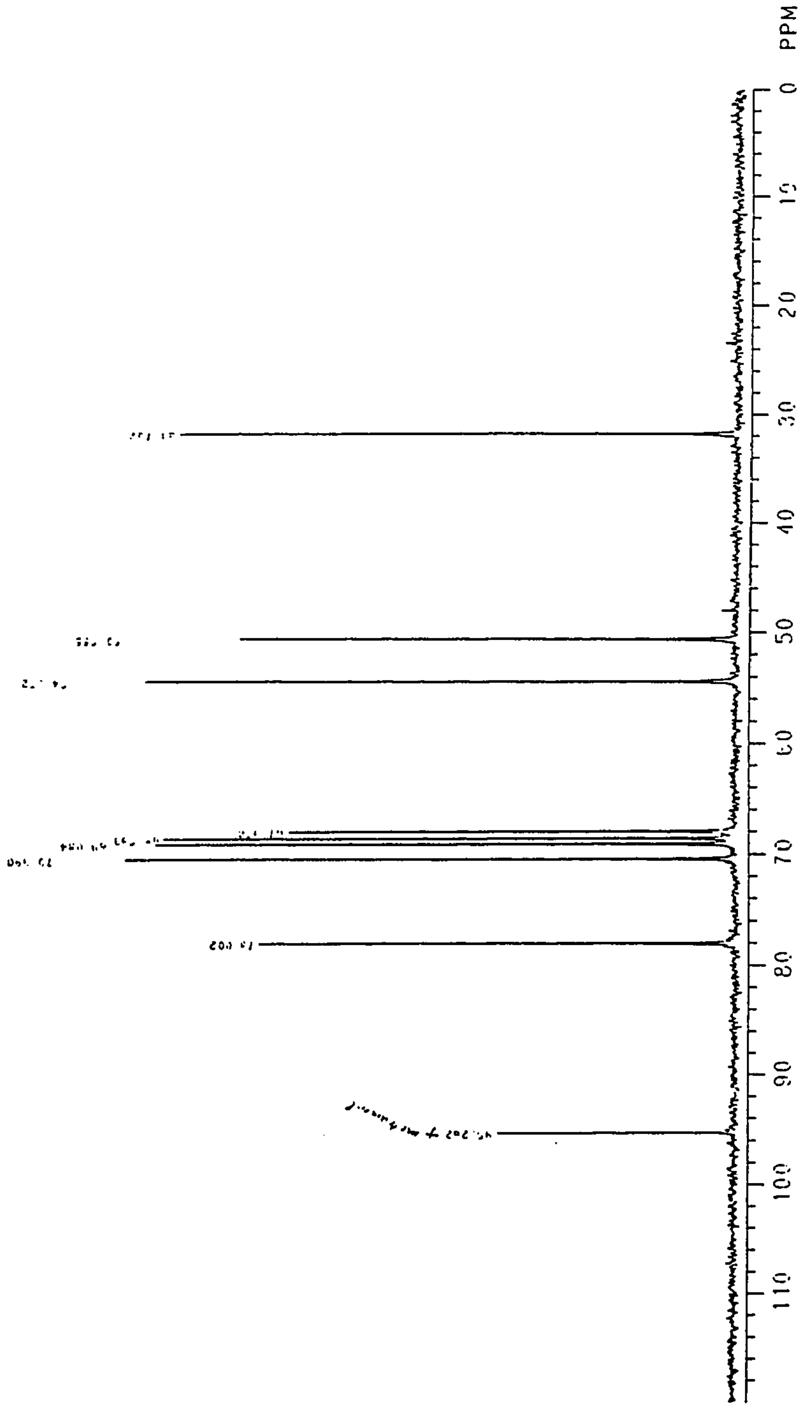

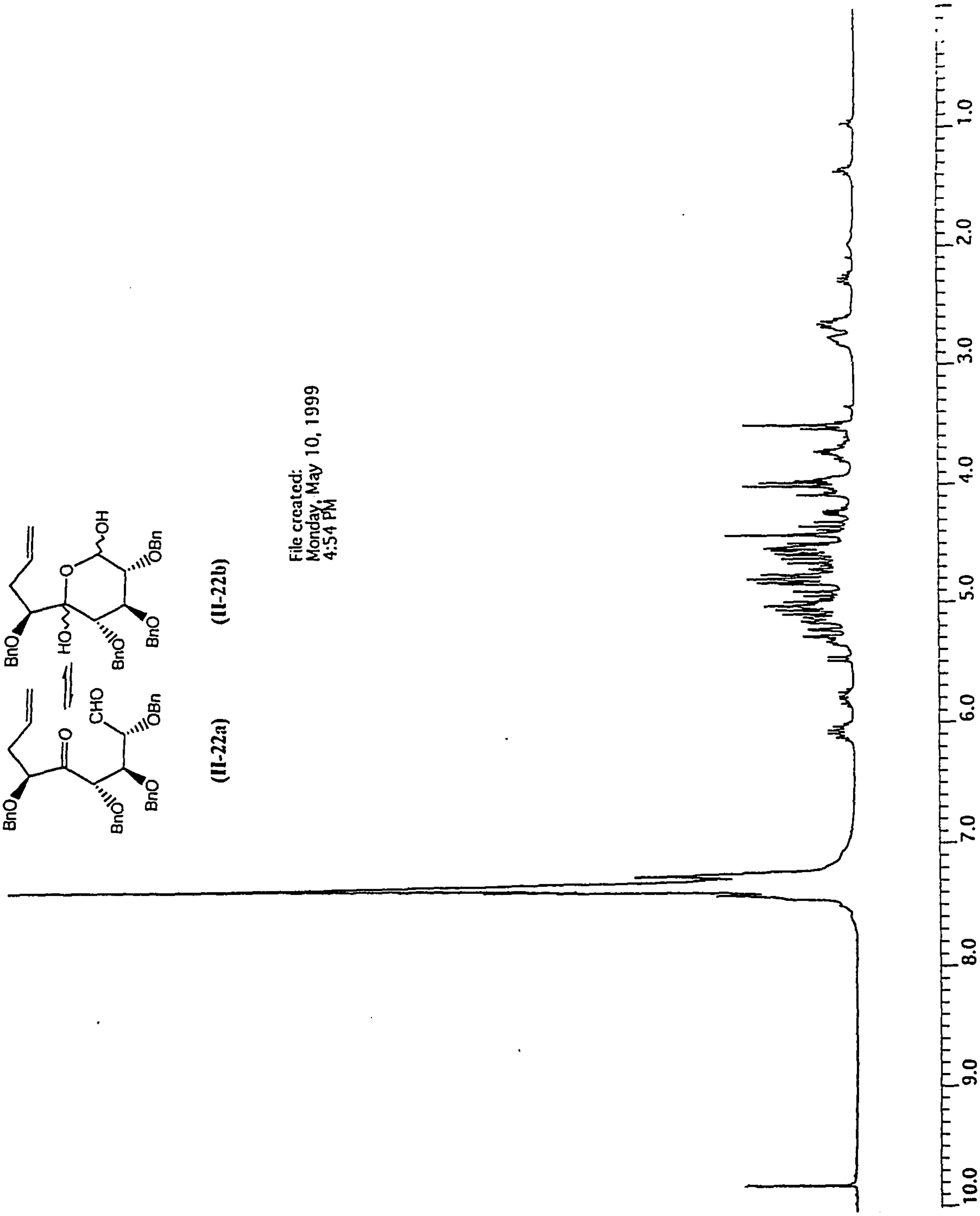

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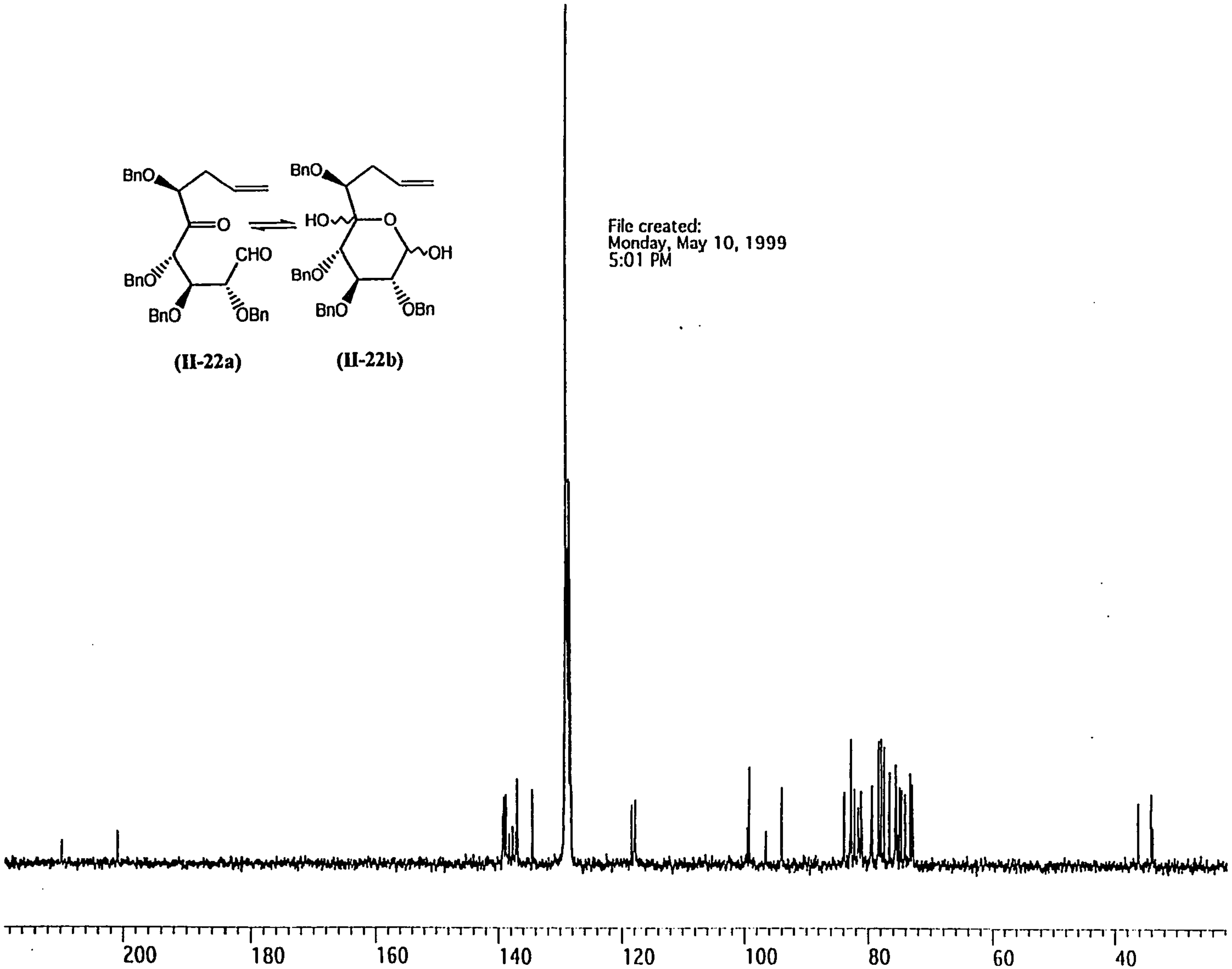

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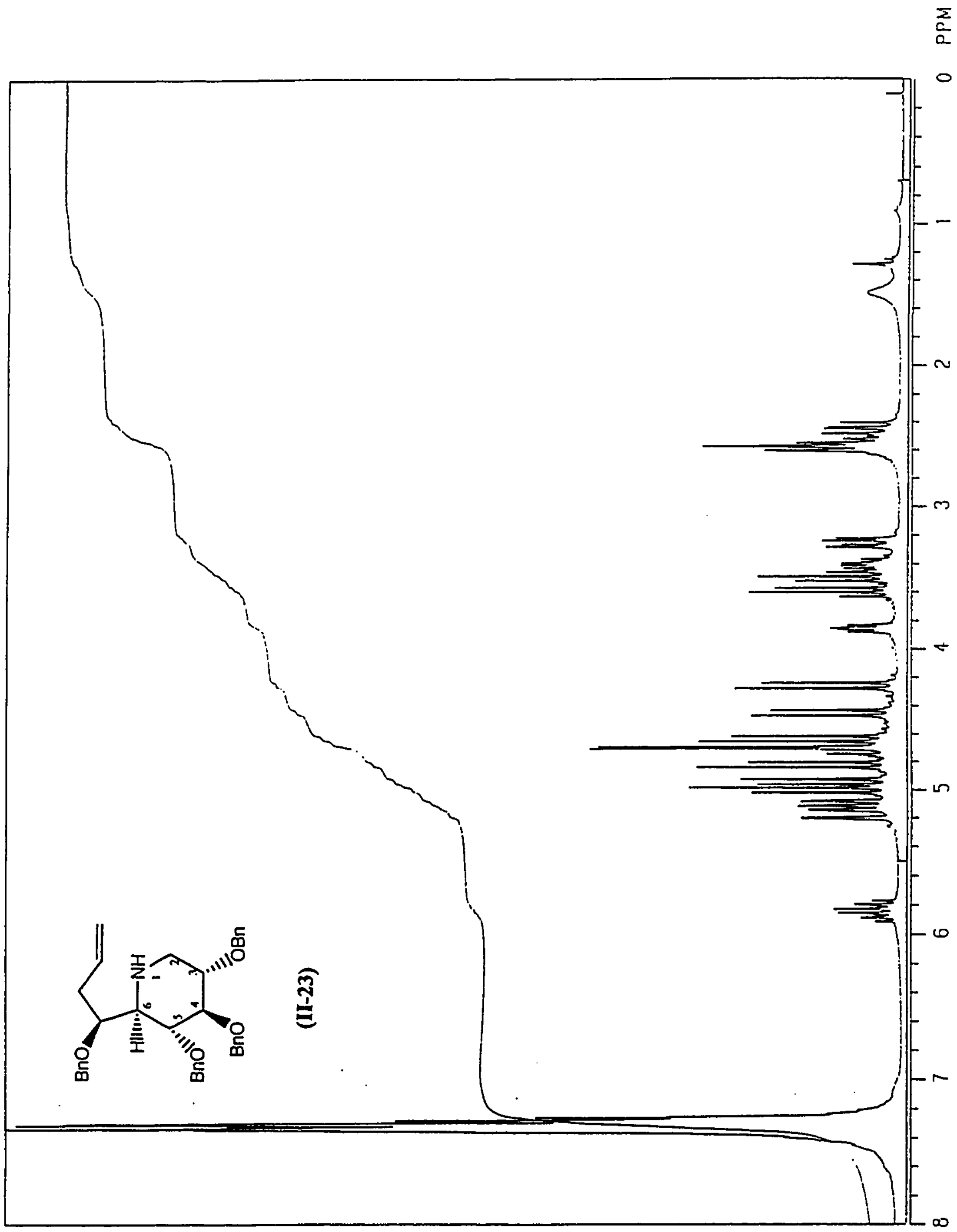

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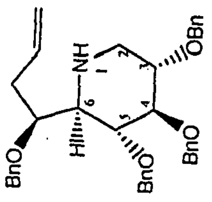

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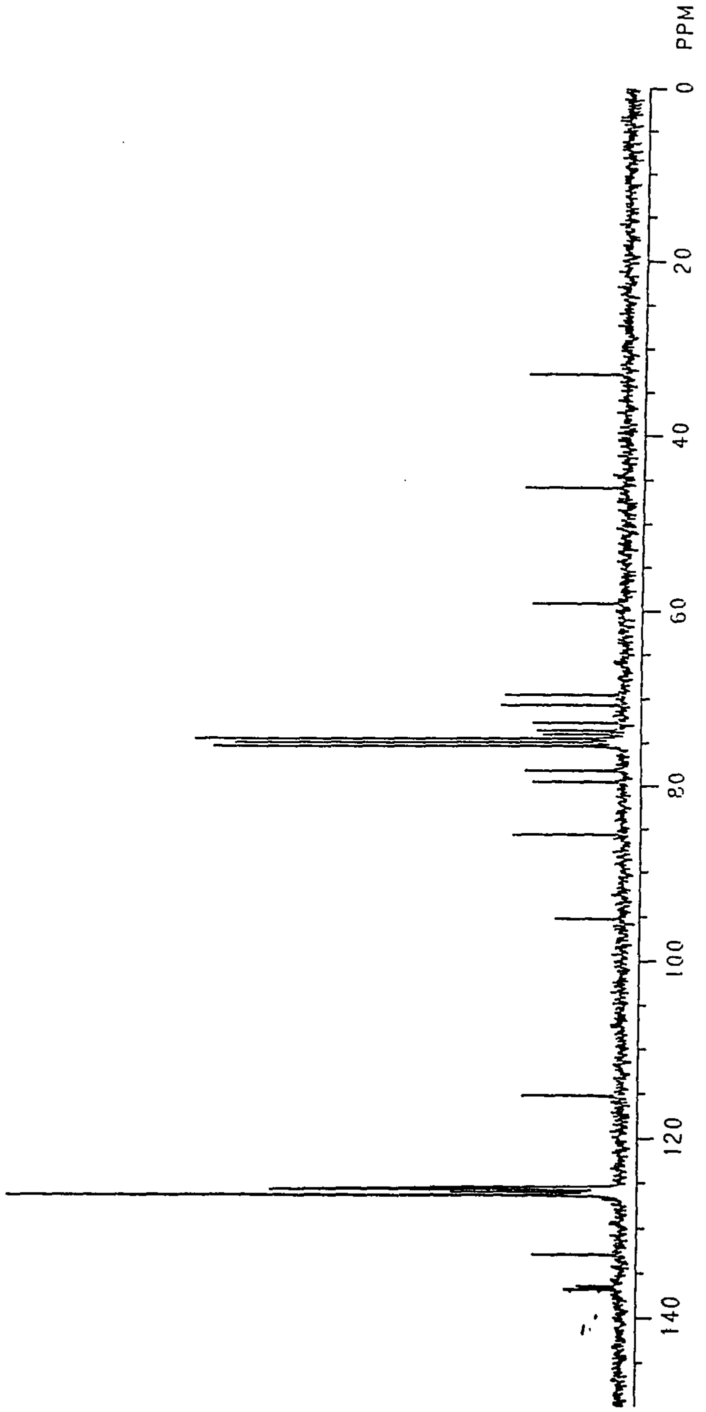

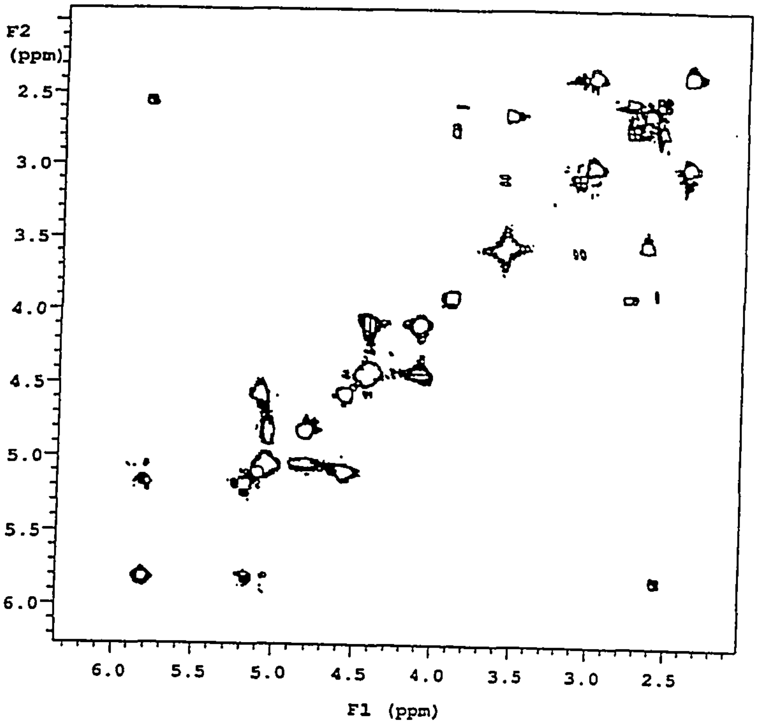
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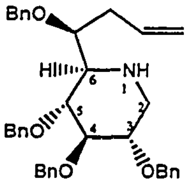
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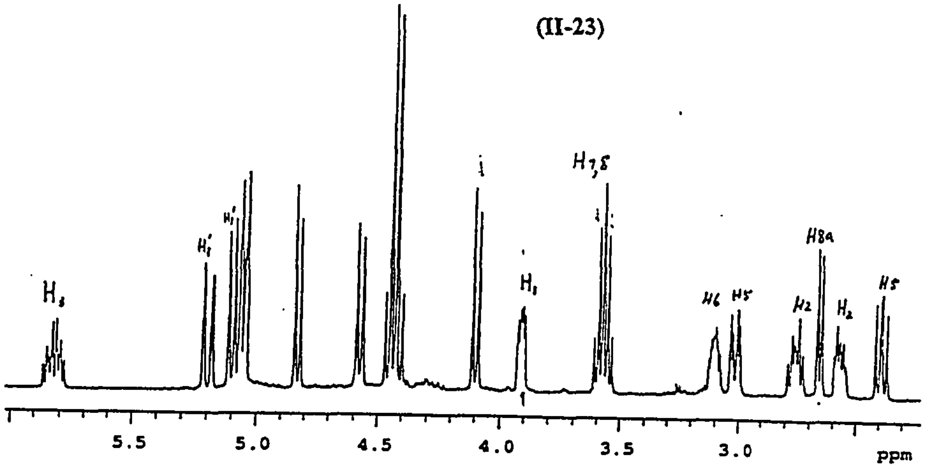
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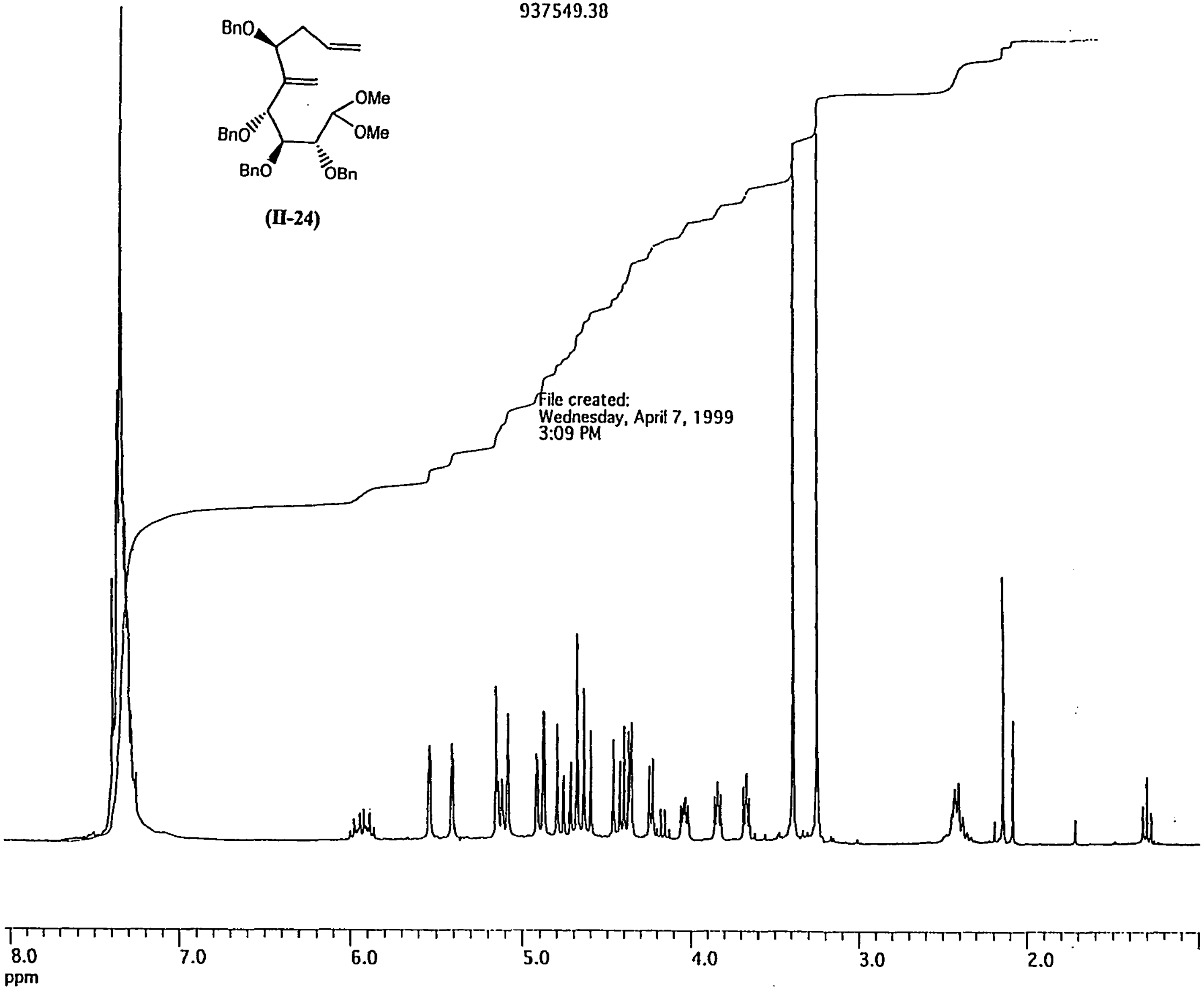
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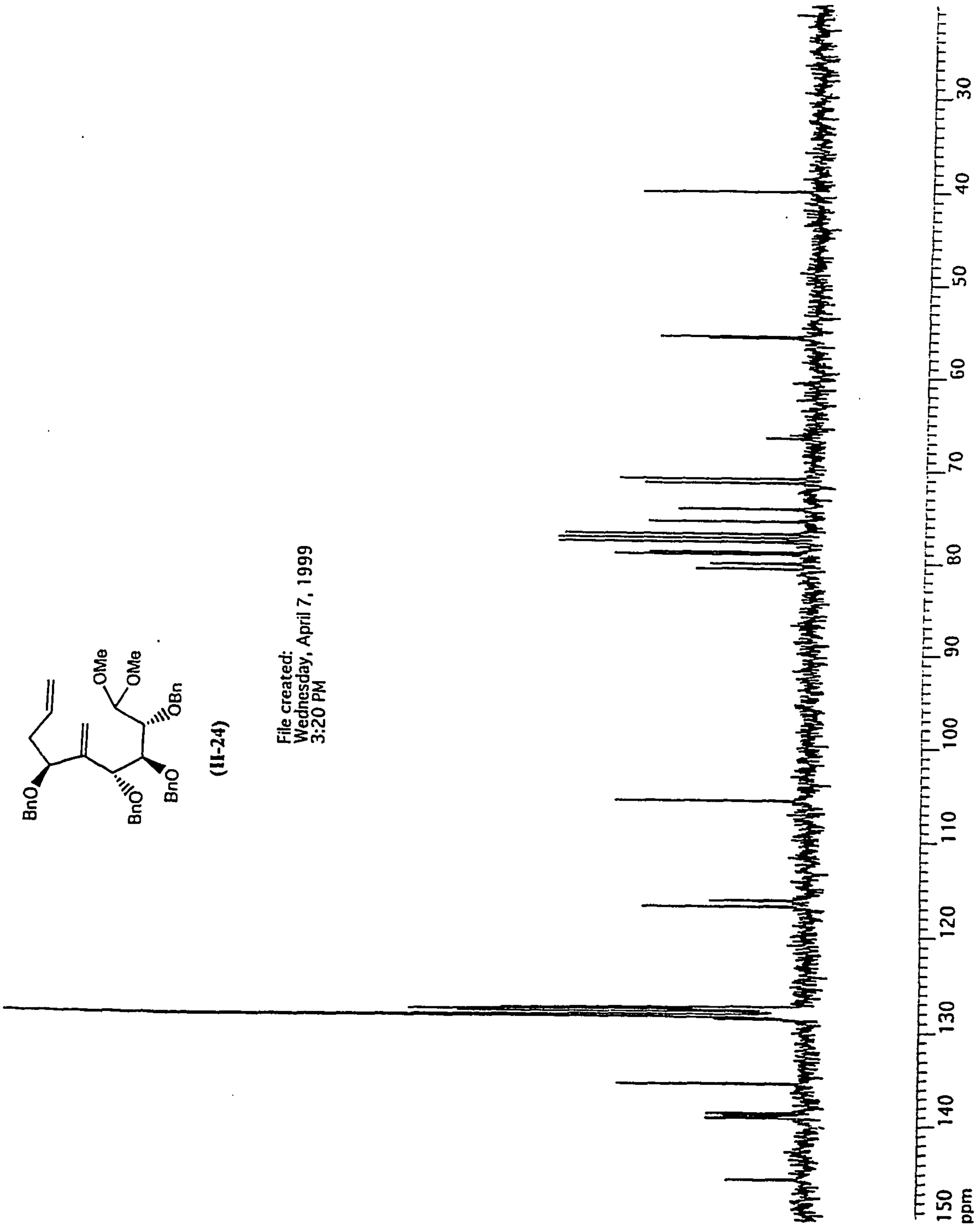
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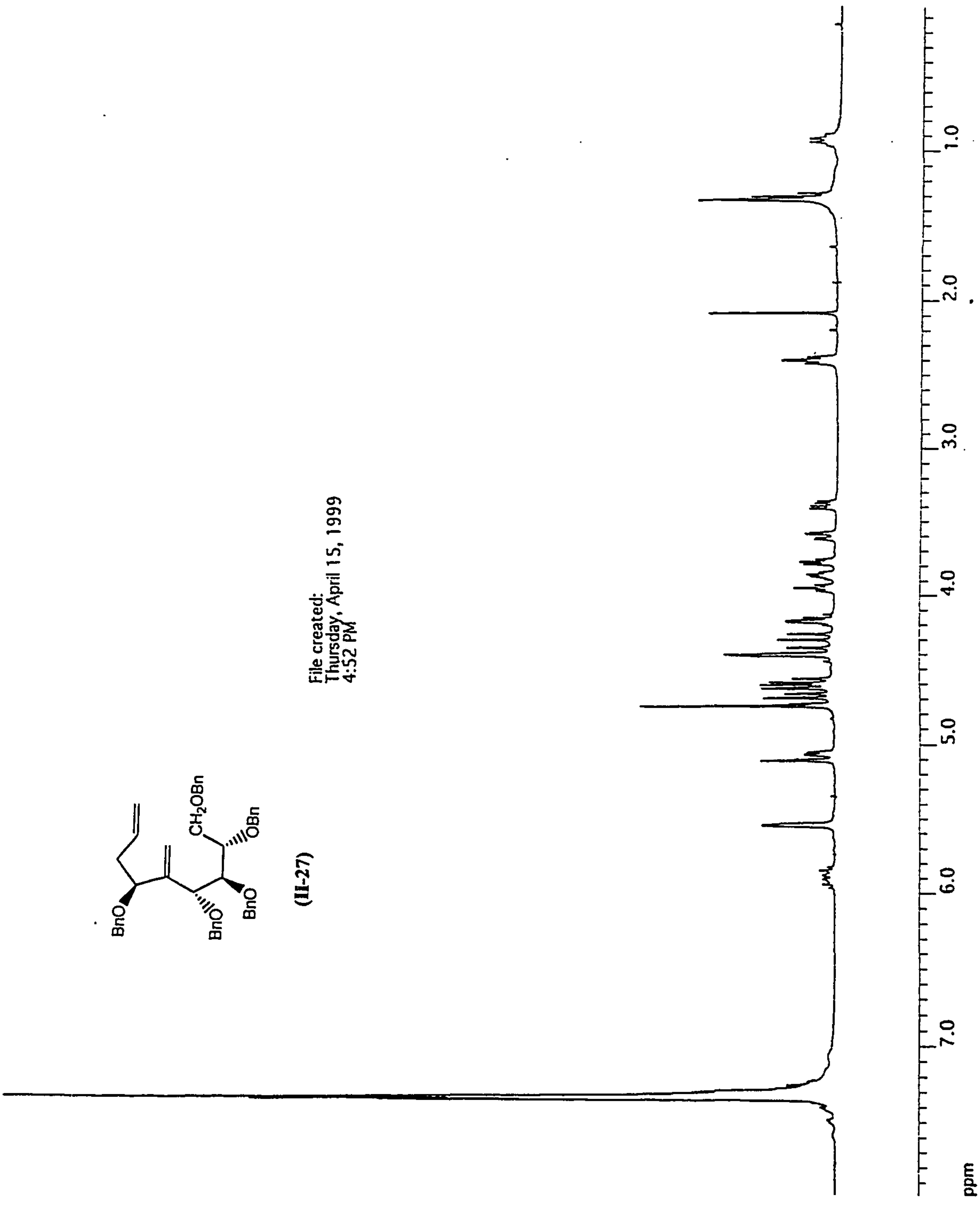
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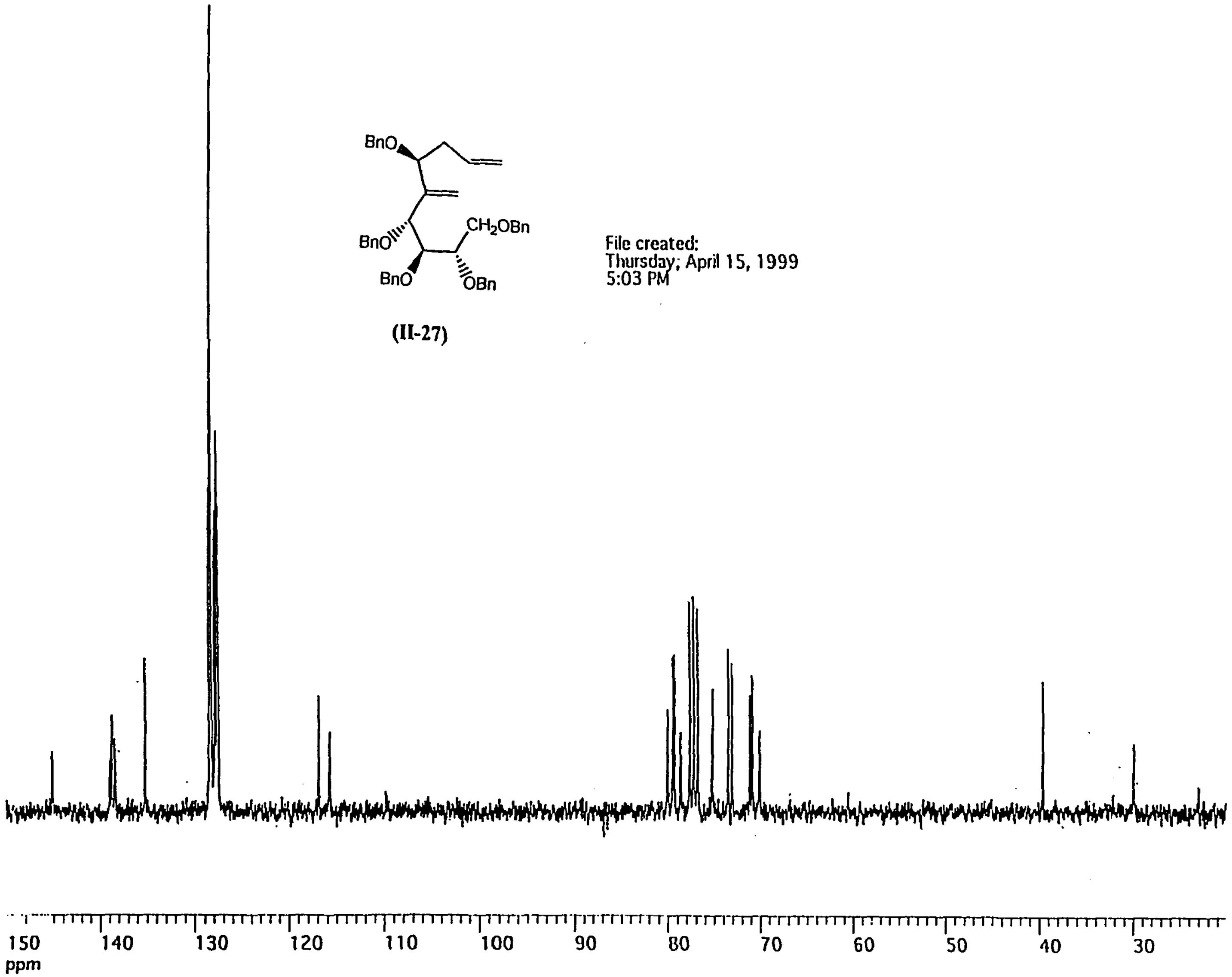
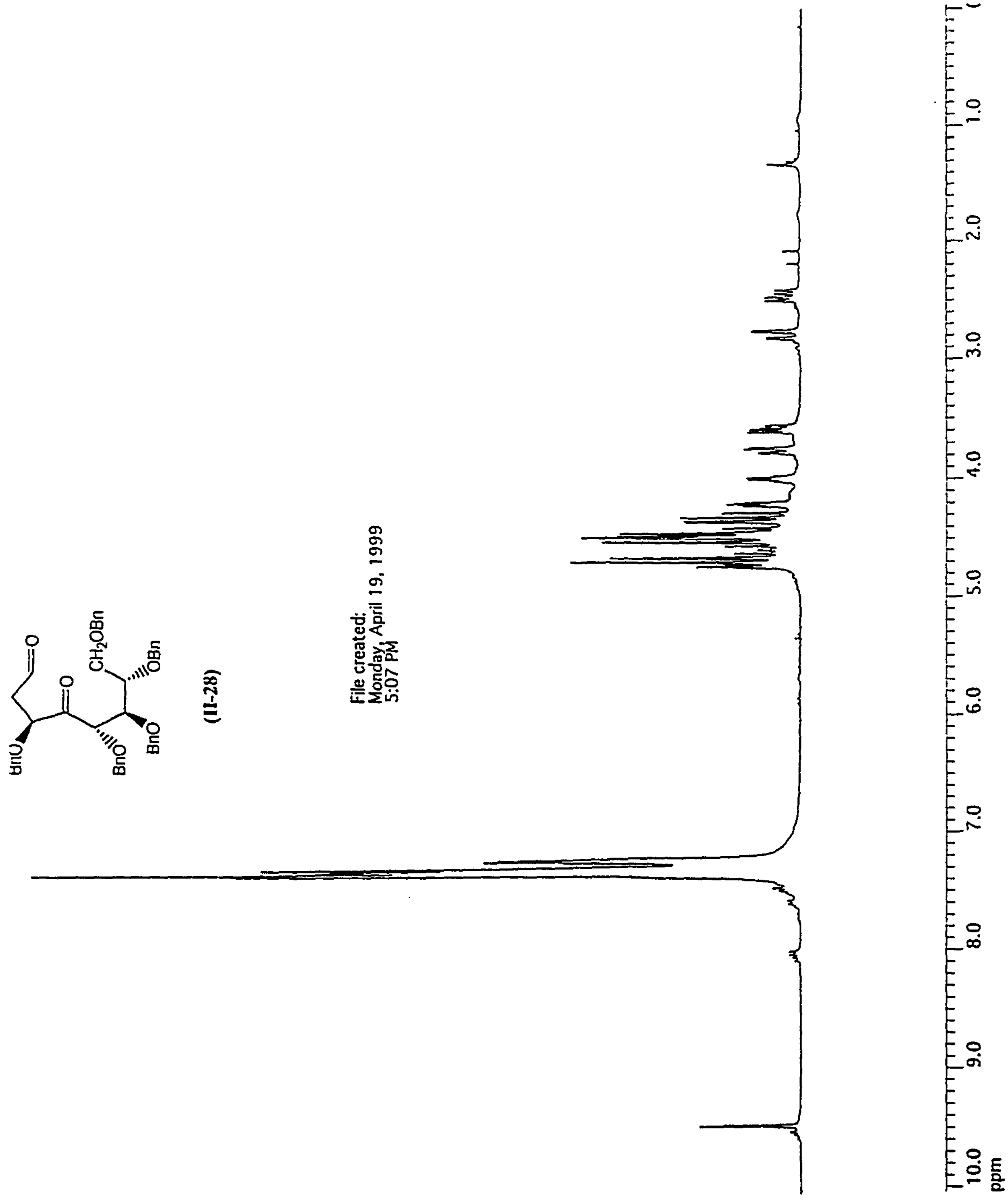
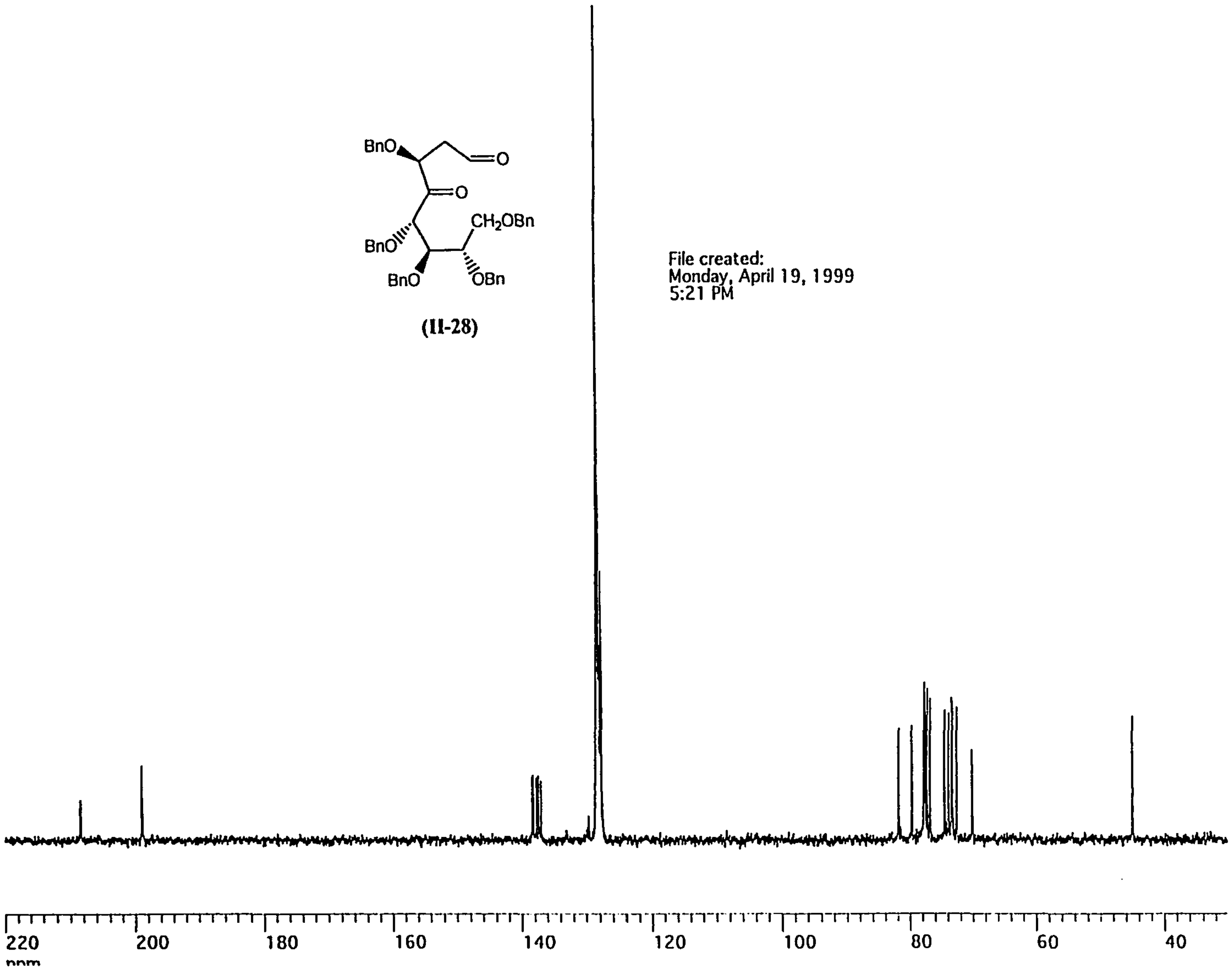


(II-27)

File created:
Thursday; April 15, 1999
5:03 PM


BnO
BnO
BnO
O
O
CH2OBn
OBn
(II-28)
File created:
Monday, April 19, 1999
5:07 PM
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
ppm



(II-28)

File created:
Monday, April 19, 1999
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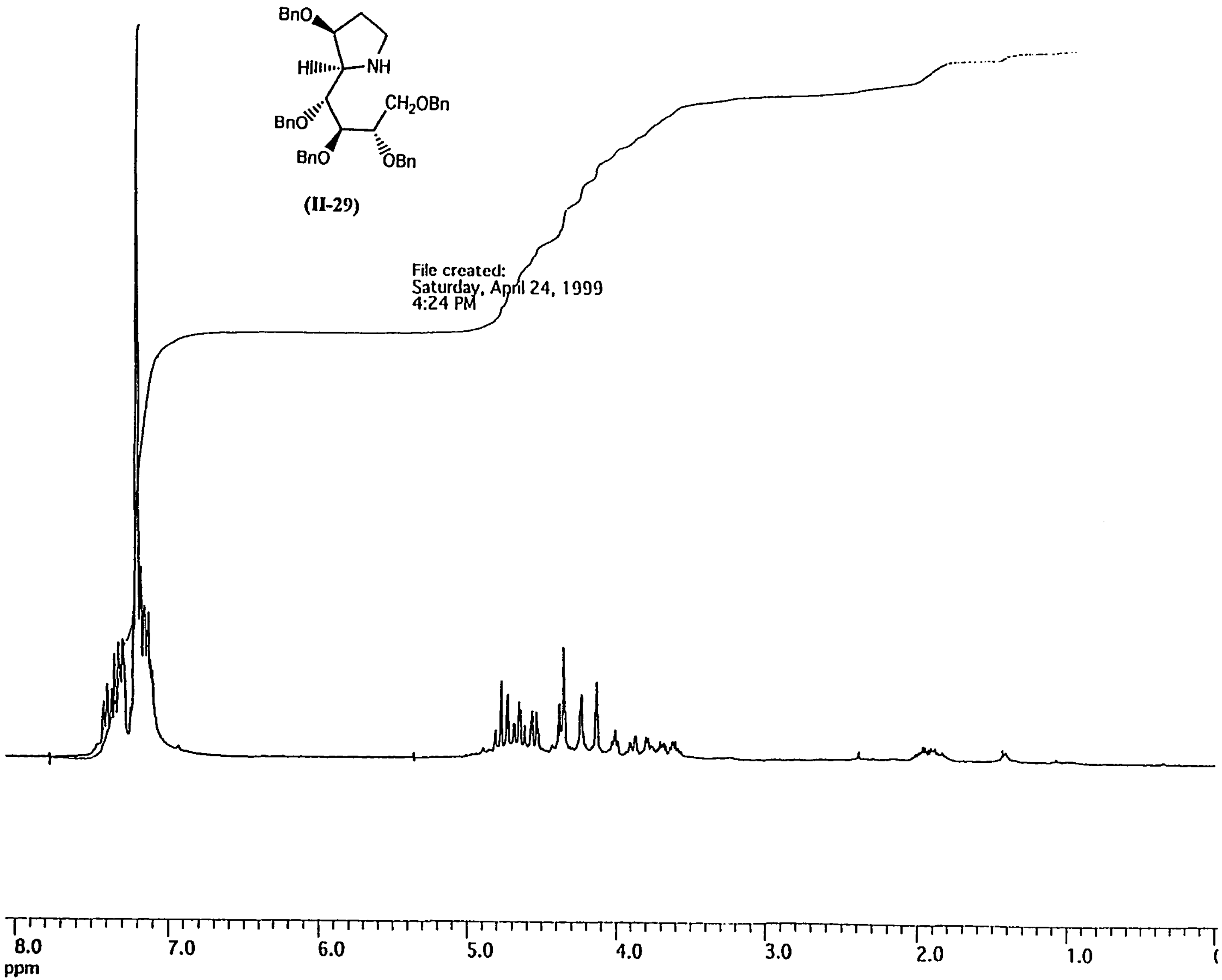
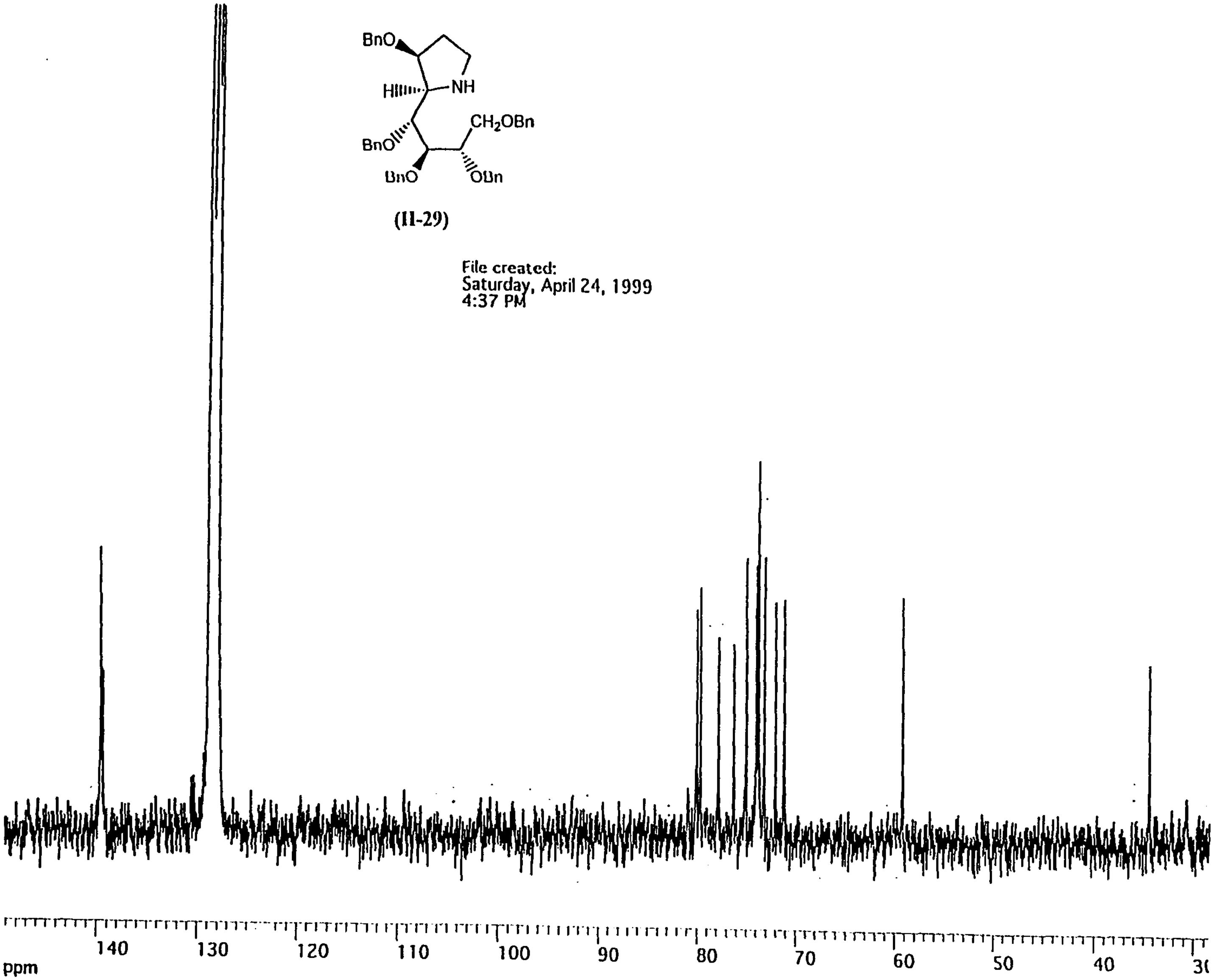

BnO
HIIII
NH
CH2OBn
BnO
BnO
OBn
File created:
Saturday, April 24, 1999
4:24 PM
8.0
ppm
7.0
6.0
5.0
4.0
3.0
2.0
1.0

(II-29)



(II-29)

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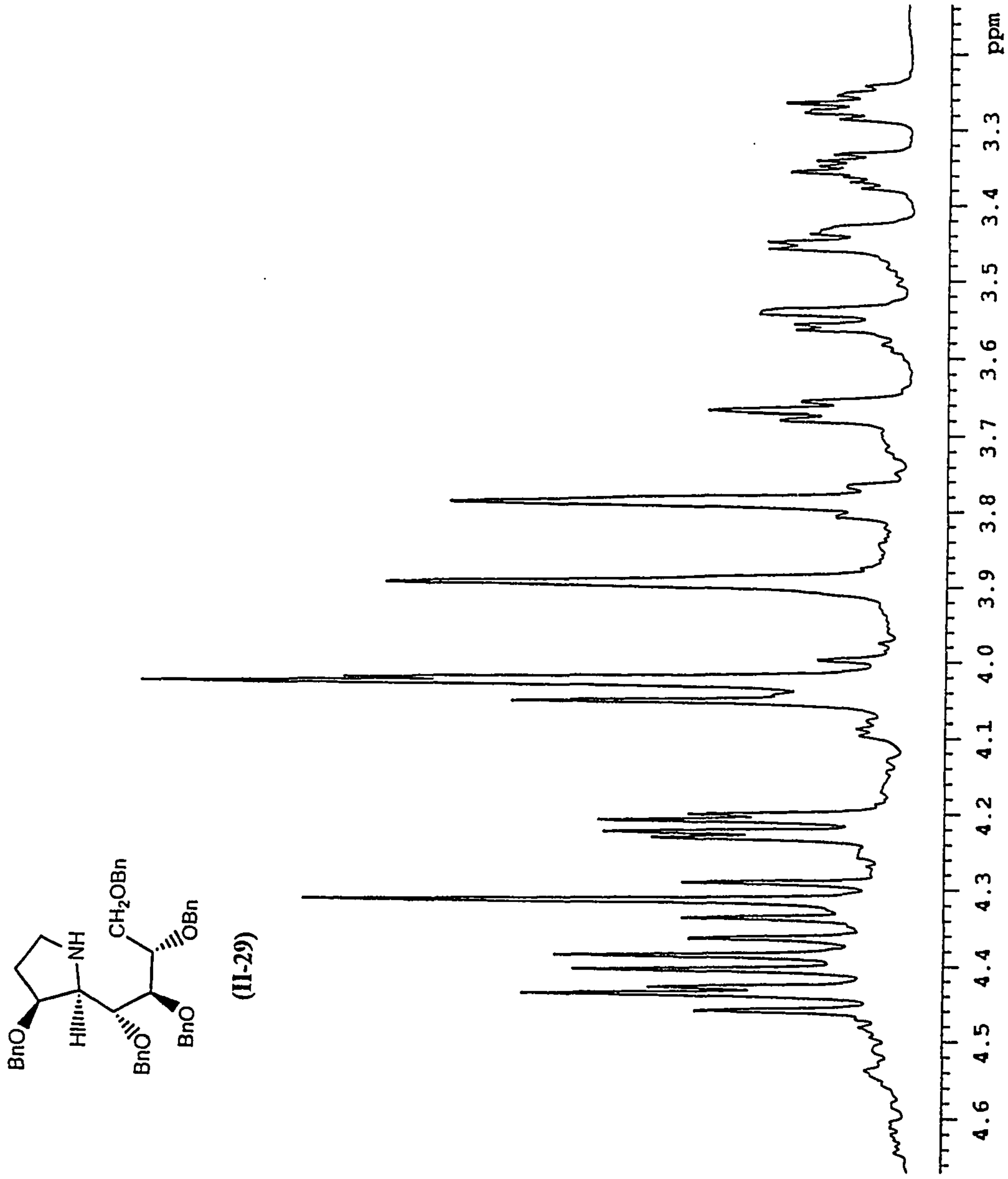
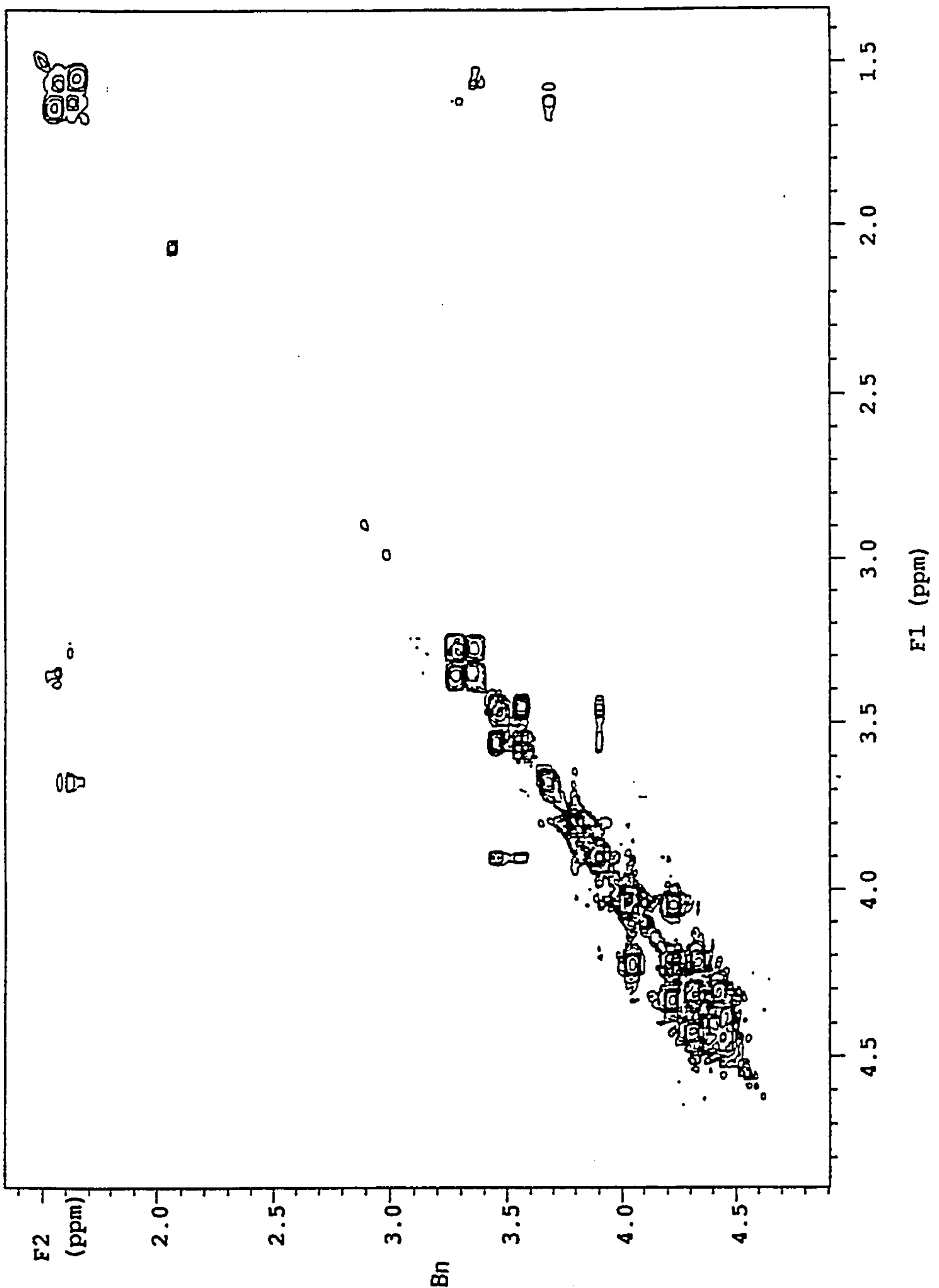
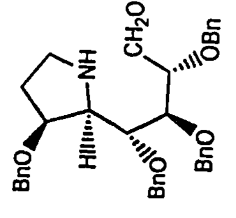
Saturday, April 24, 1999
4:37 PM

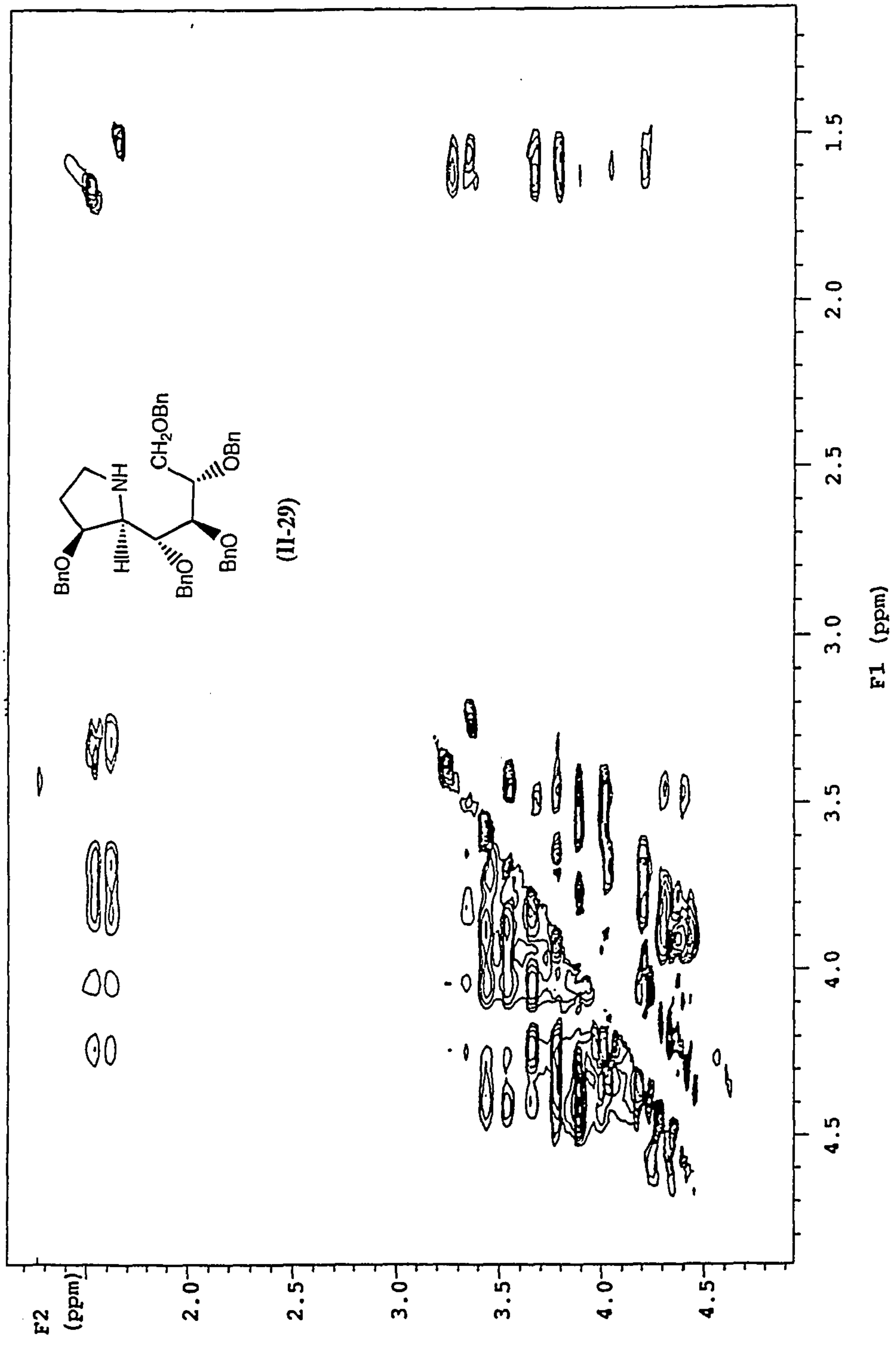

BnO
NH
CH2OBn
OBn
BnO
BnO
H
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
ppm

(II-29)

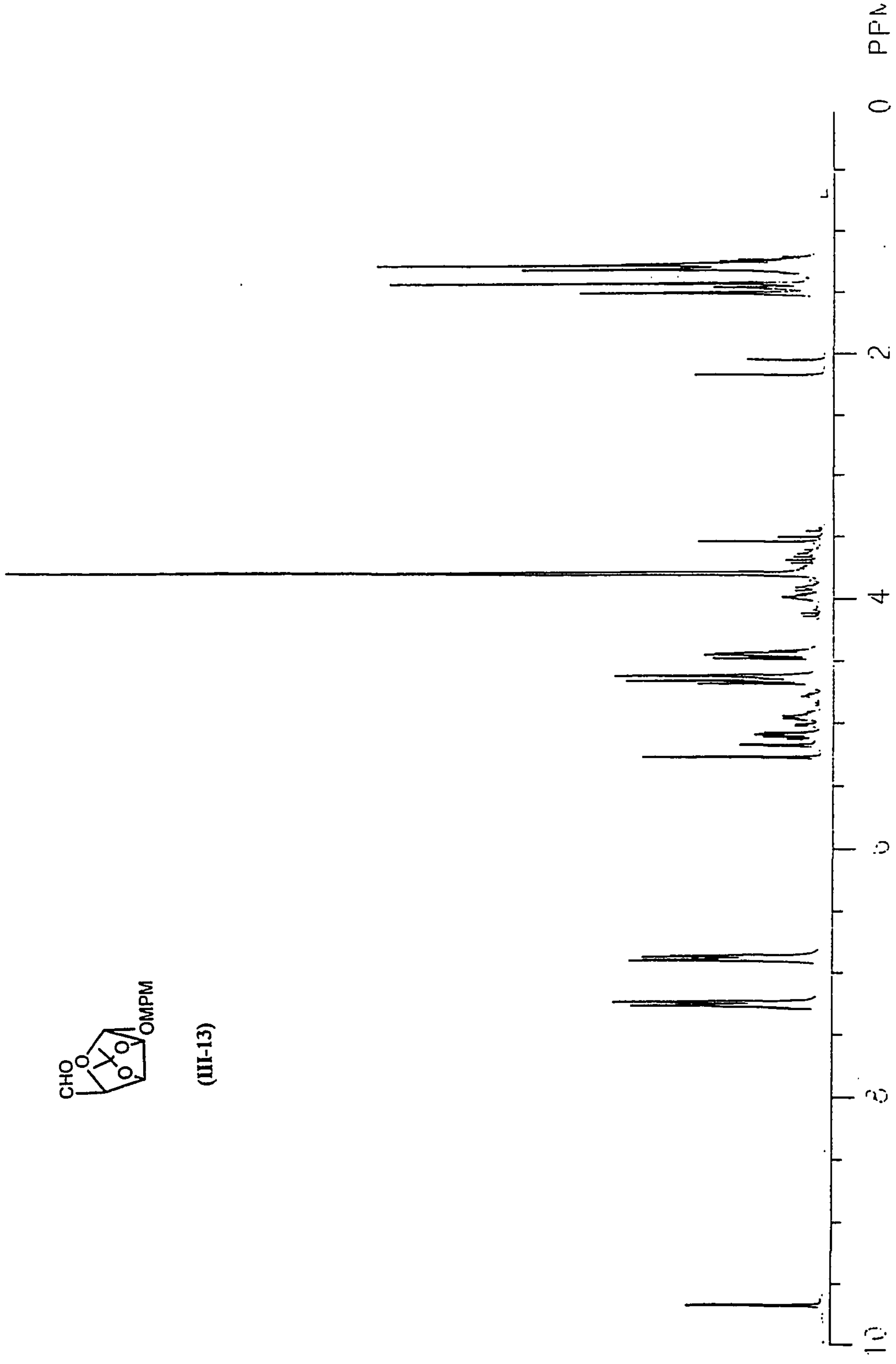

F1 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
F2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5


BnO
H
NH
CH2OBn
OBn
BnO
BnO

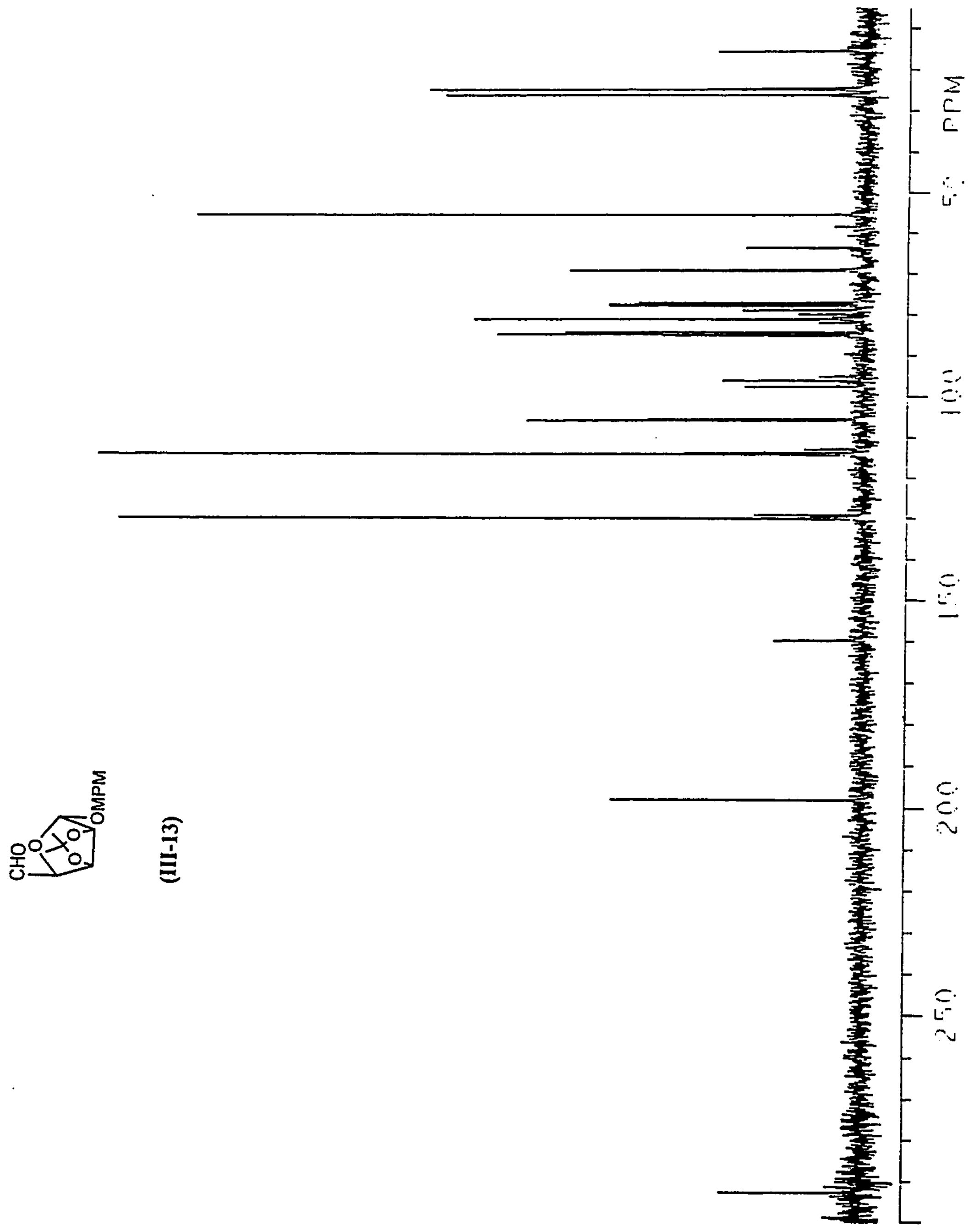
(II-29)


BnO
H
NH
CH₂OBn
OBn
BnO
BnO
F2 (ppm)
2.0
2.5
3.0
3.5
4.0
4.5
F1 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5

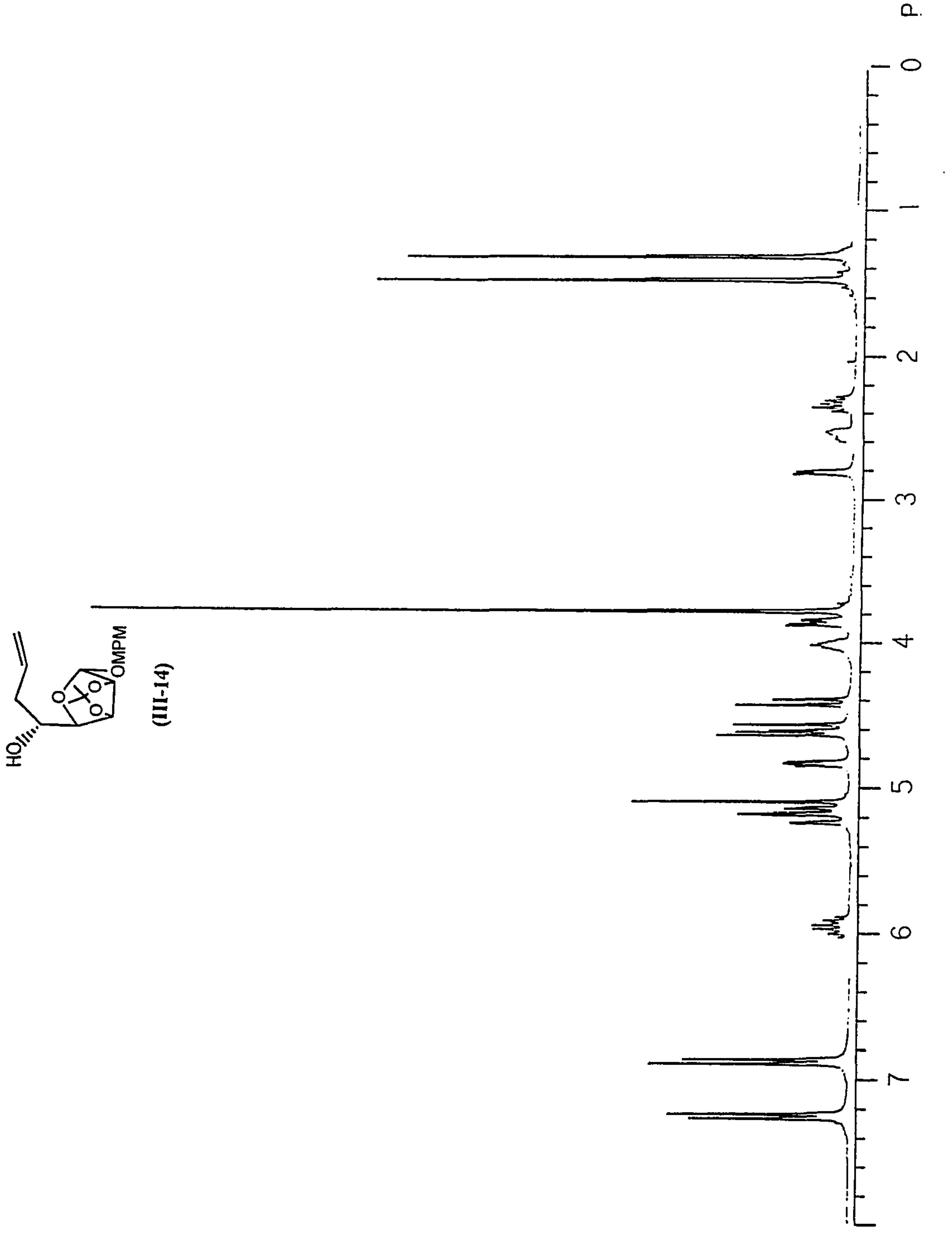
(II-29)



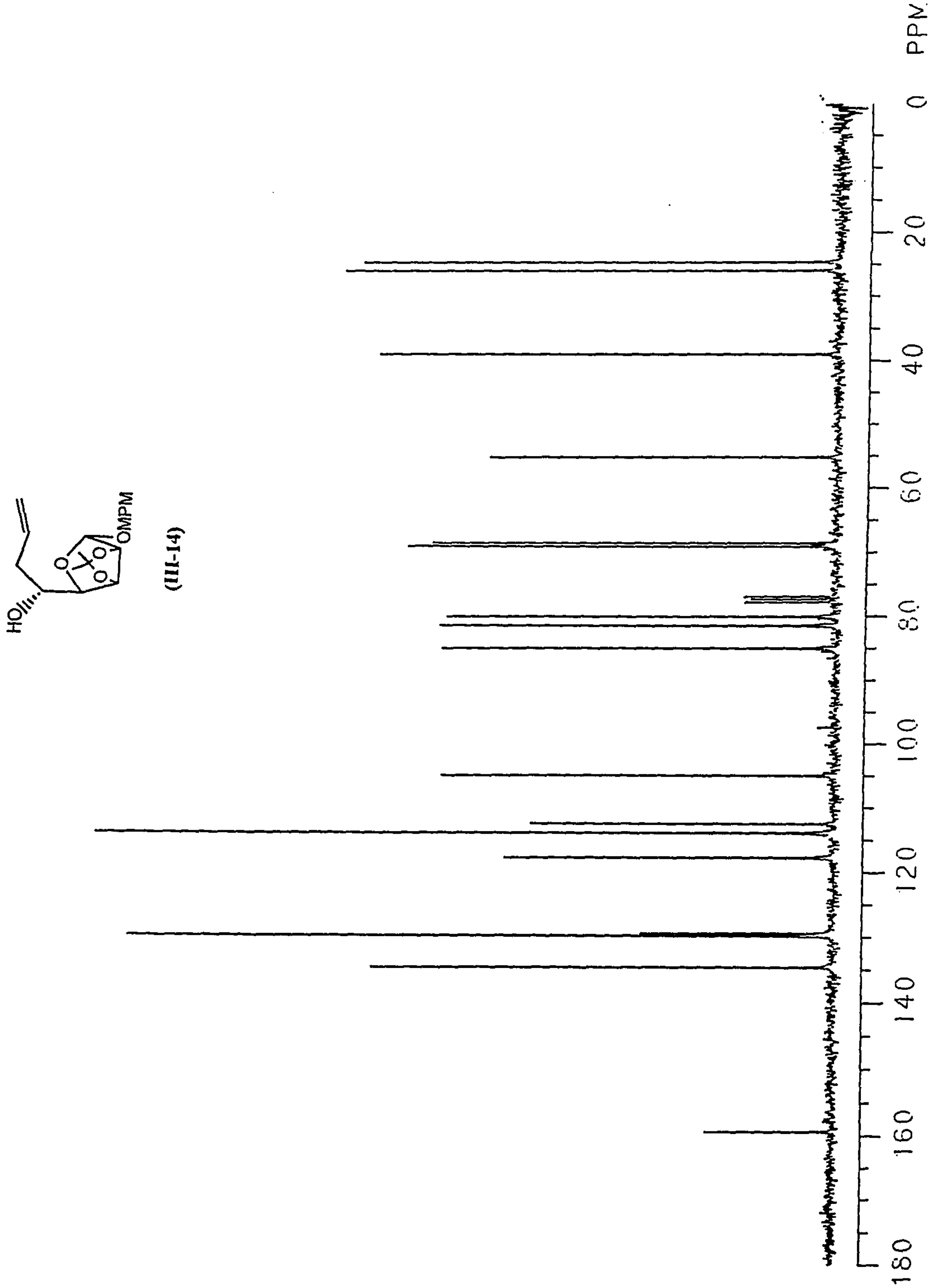
(III-13)



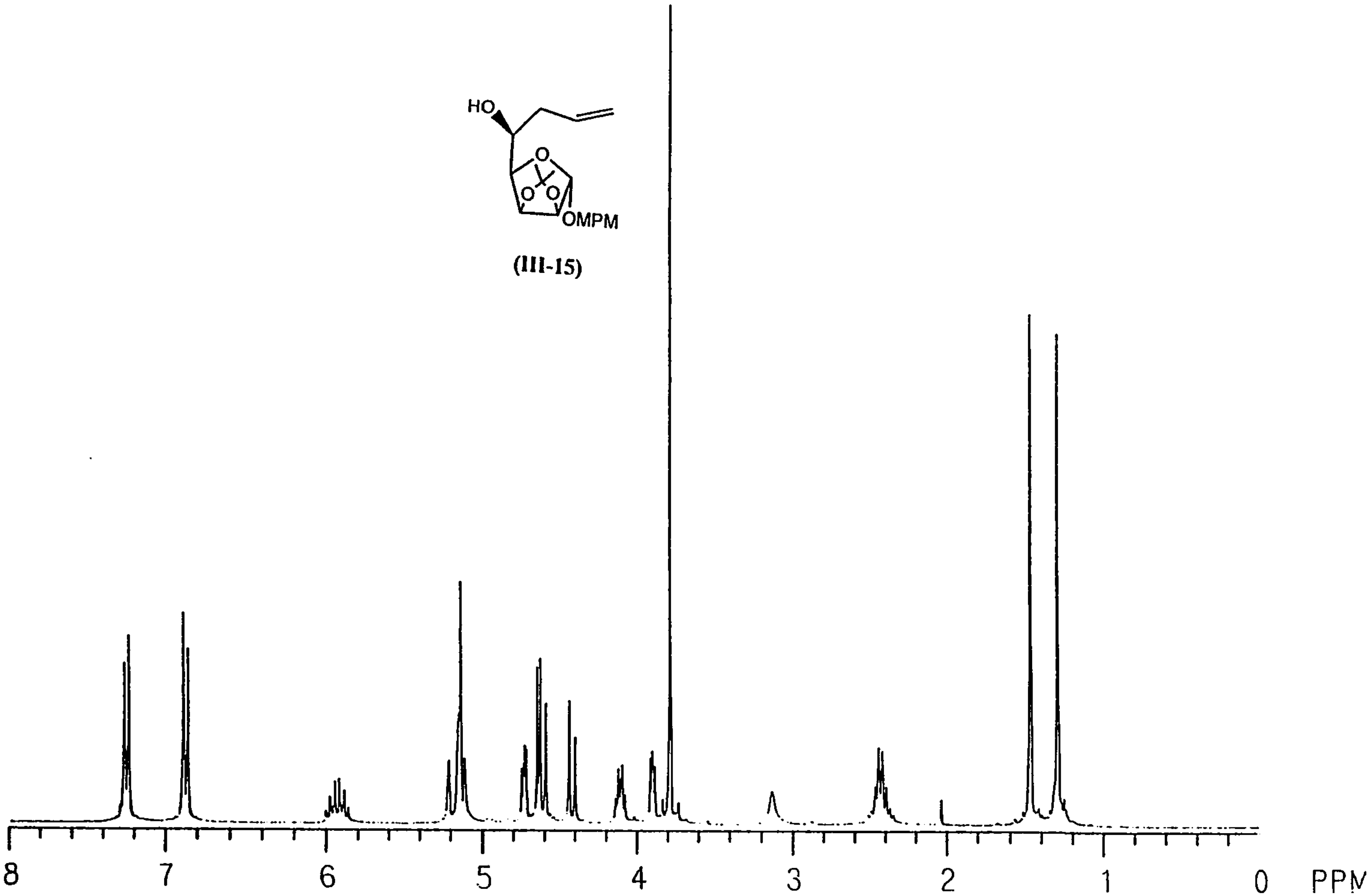
(III-13)



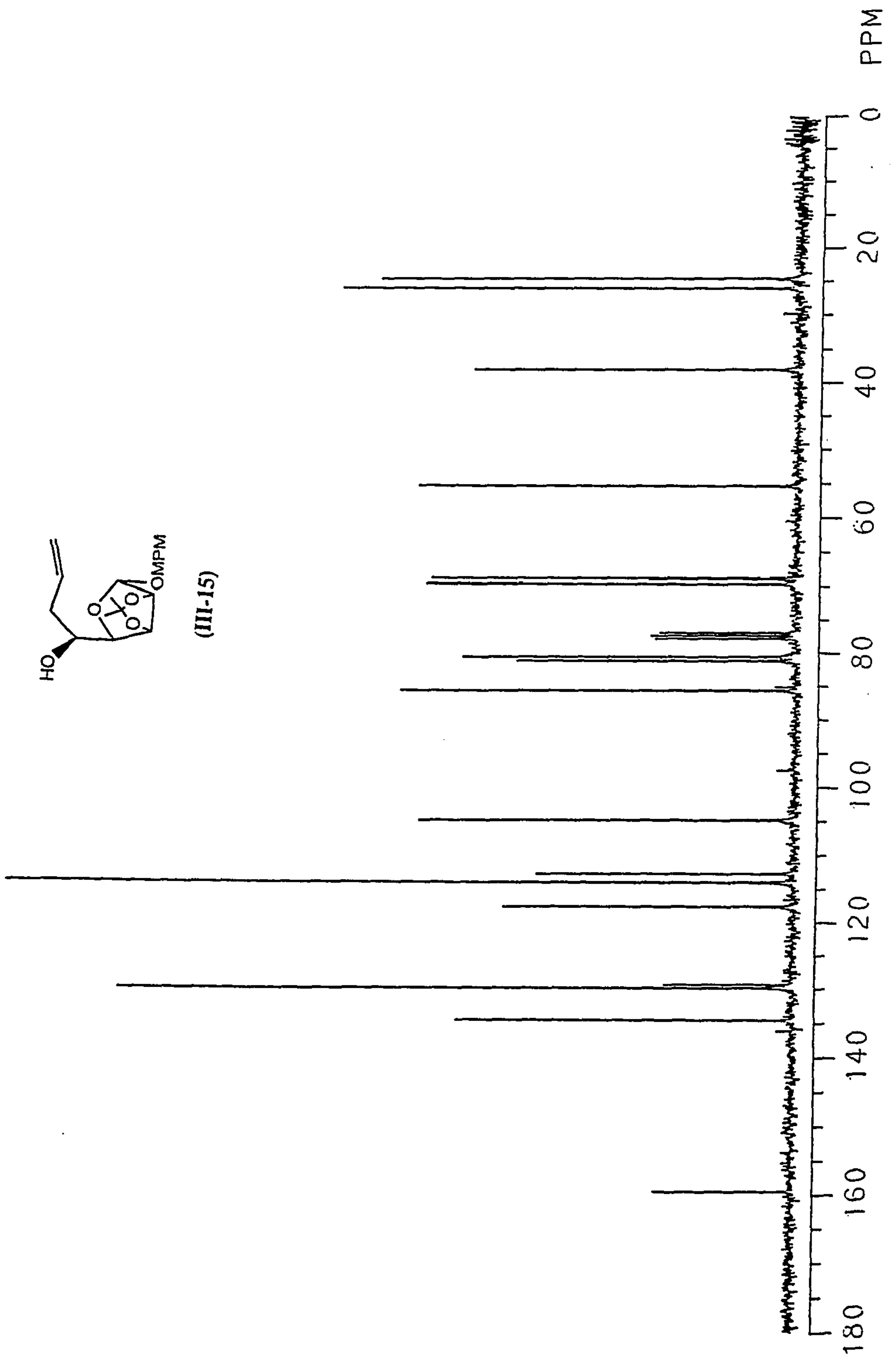
(III-14)



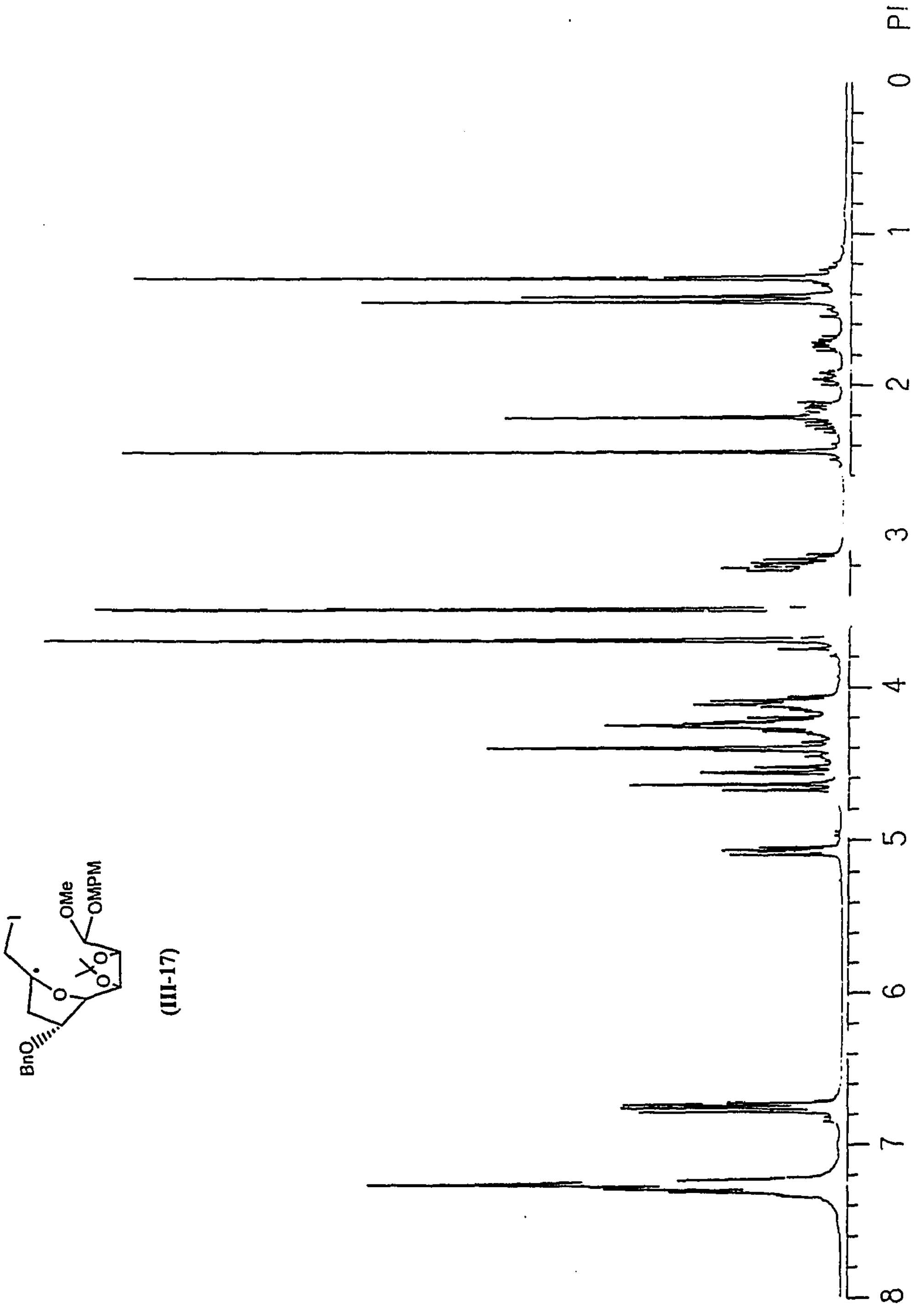
(III-14)



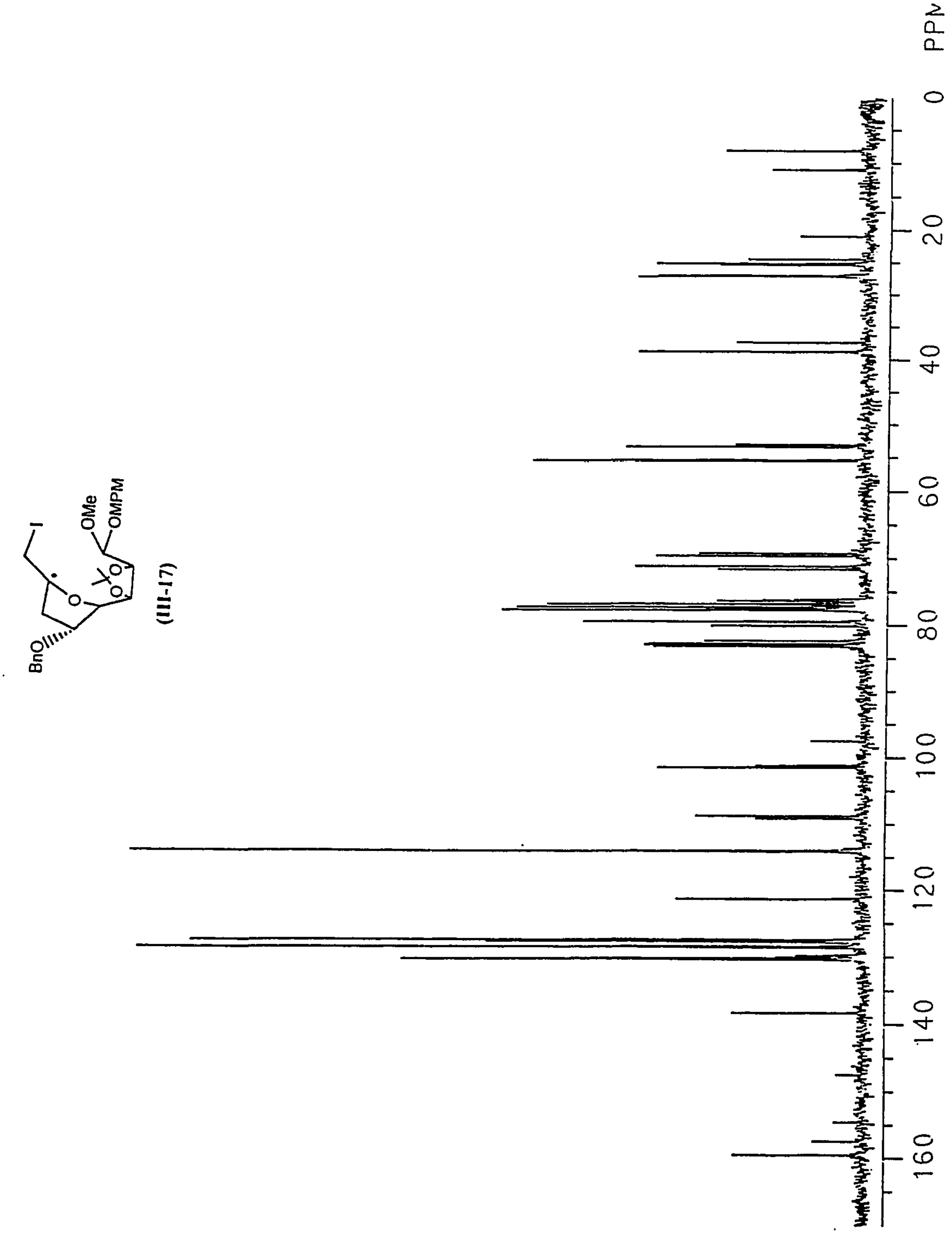
(III-15)



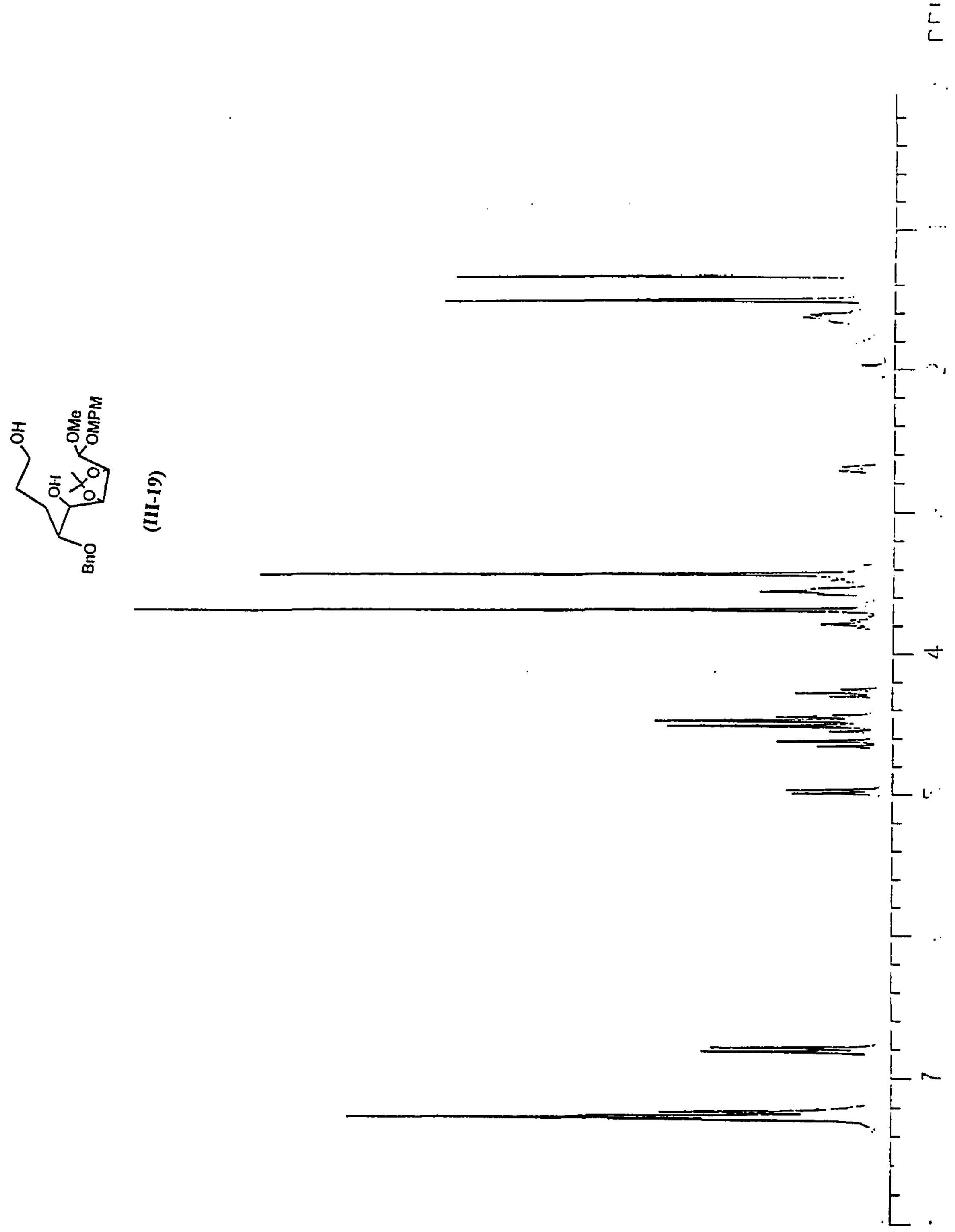
(III-15)



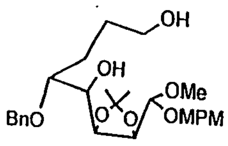
(III-17)



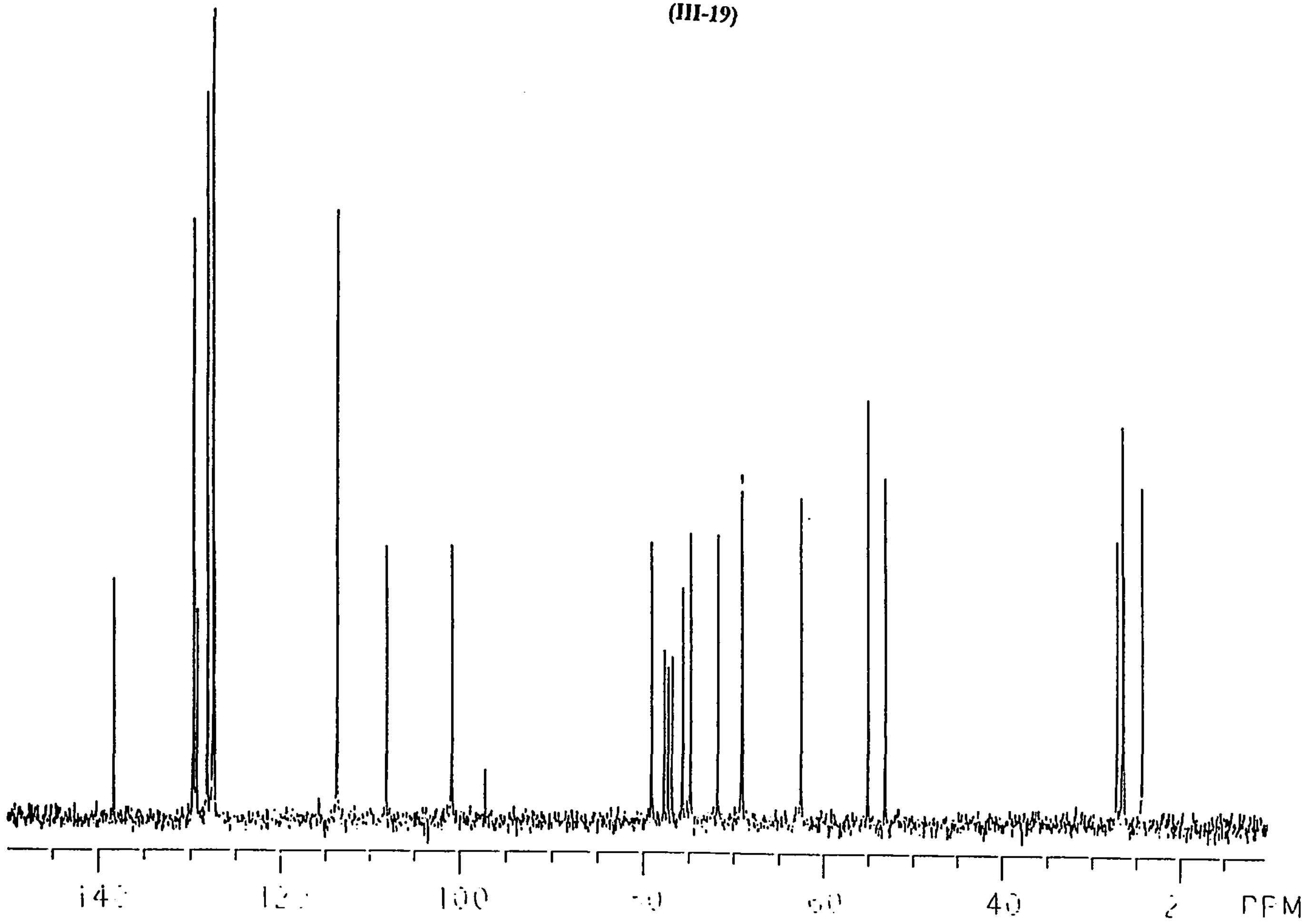
(III-17)

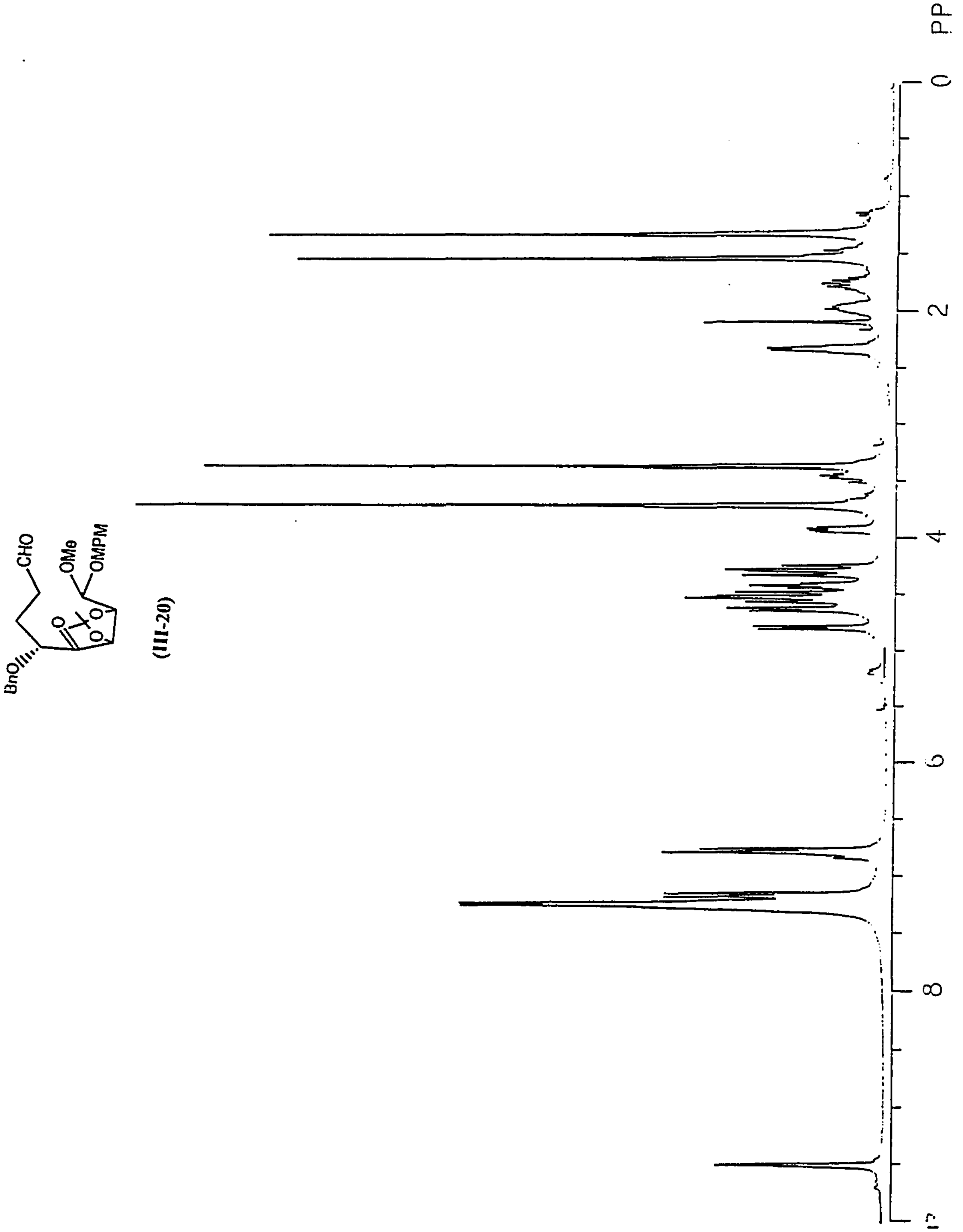


(III-19)

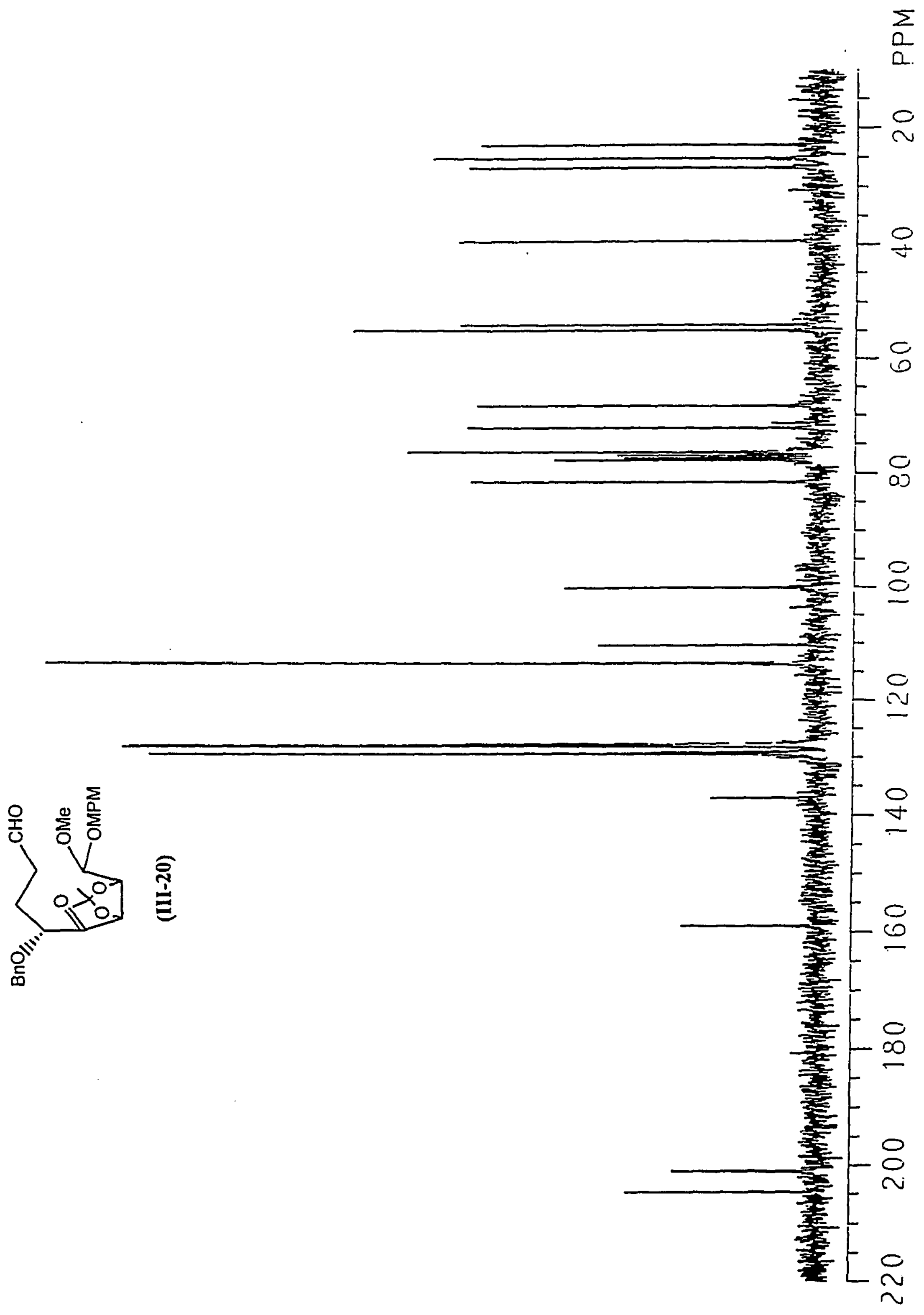


(III-19)

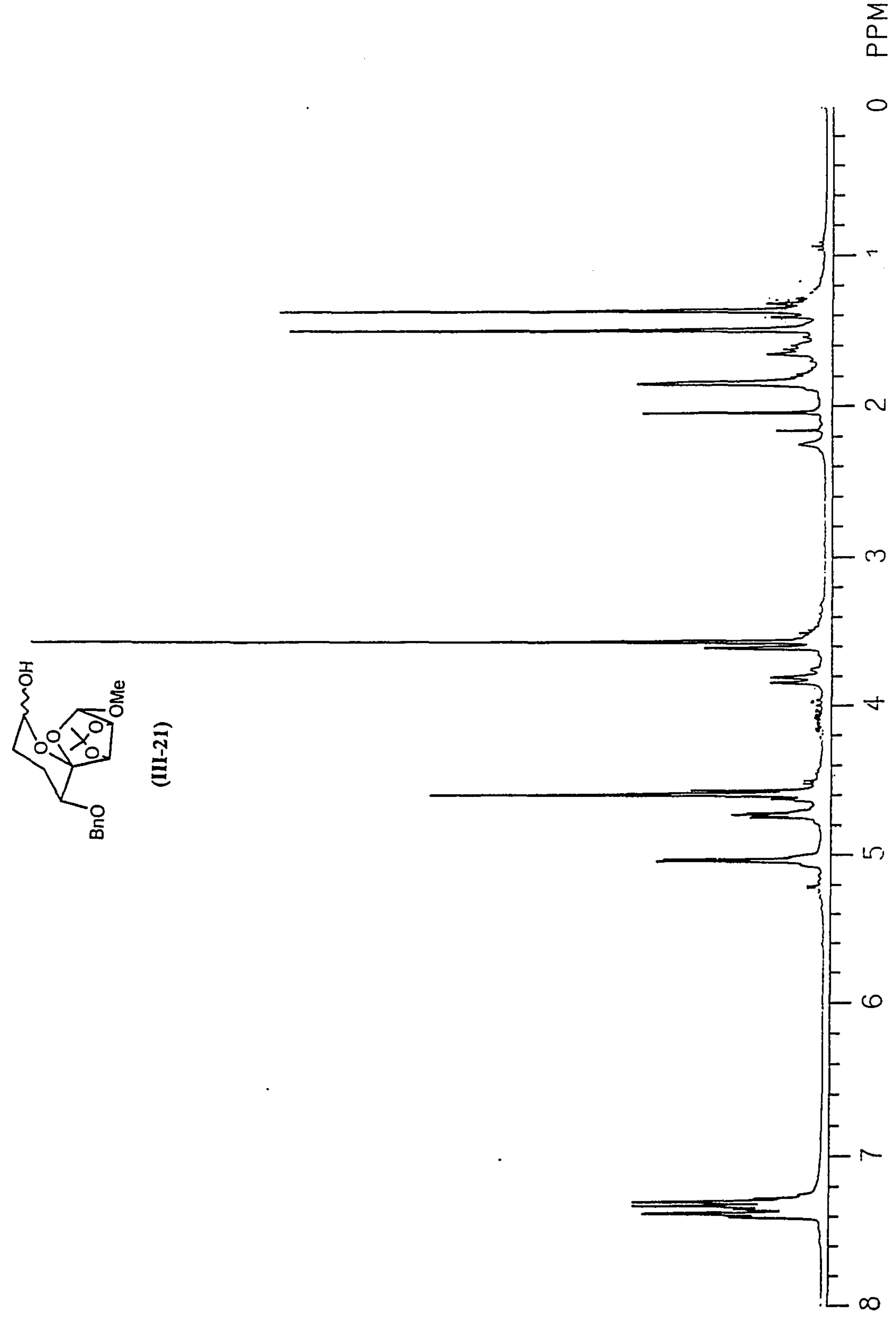




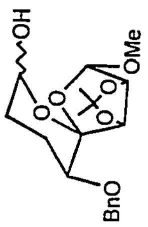
(III-20)



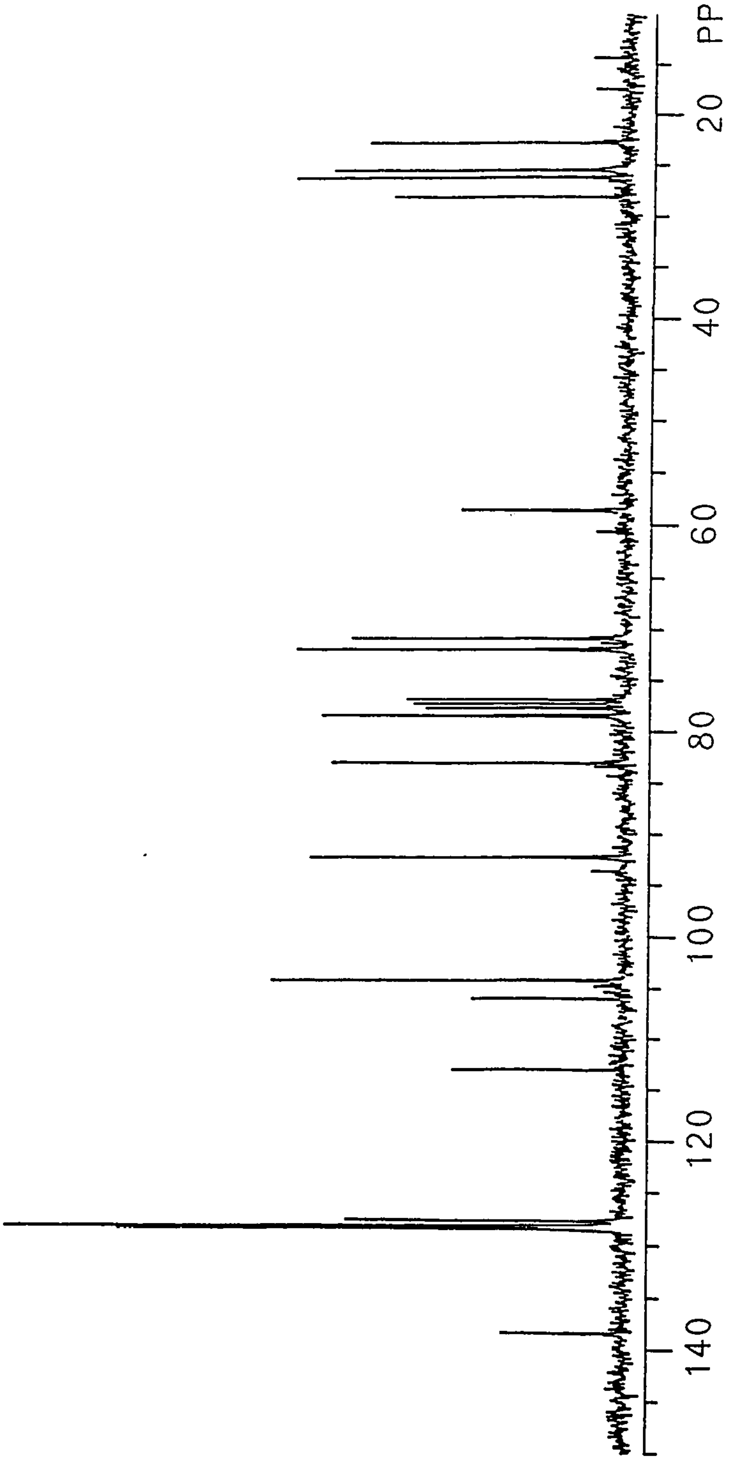
(III-20)

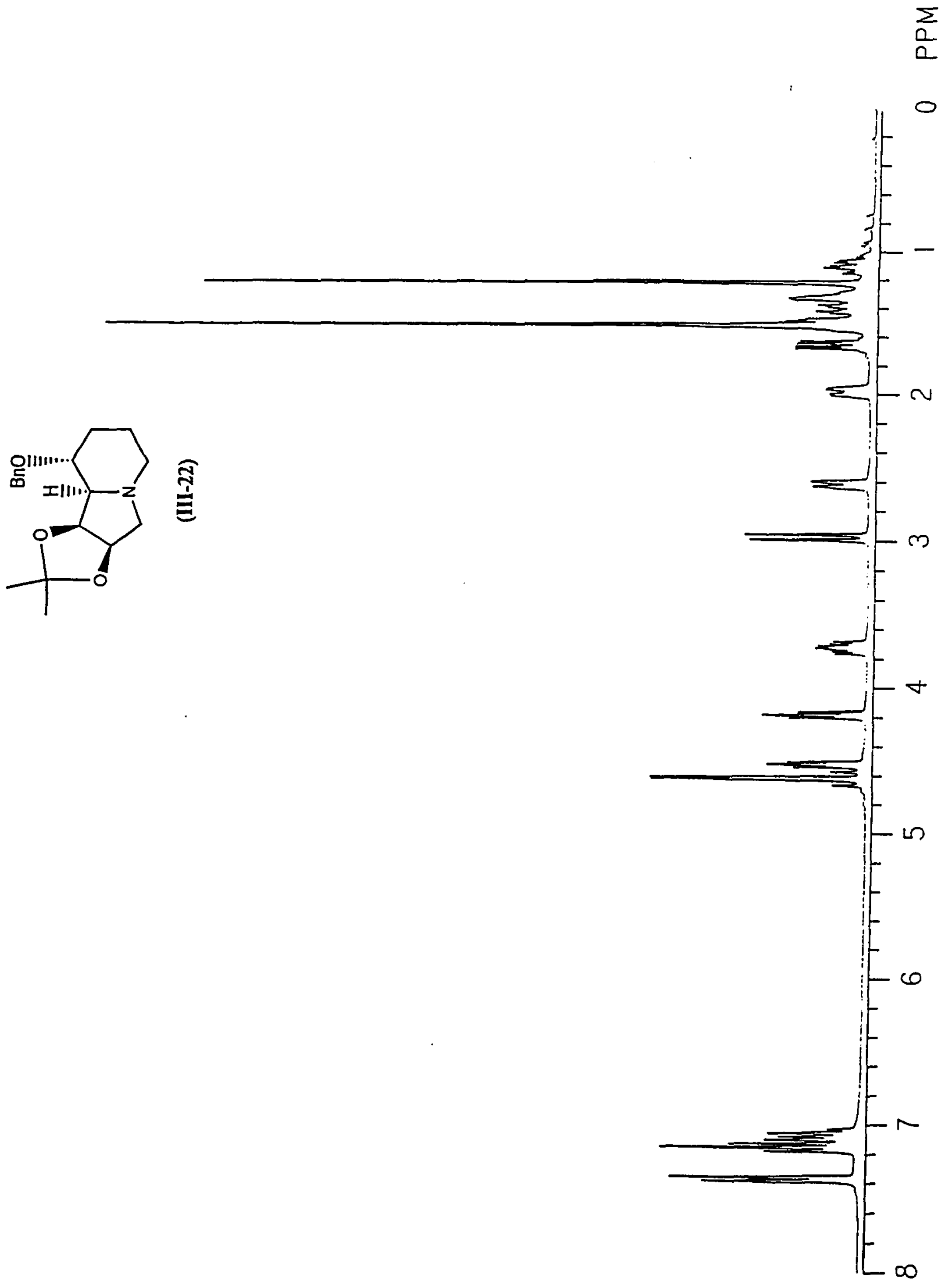


(III-21)

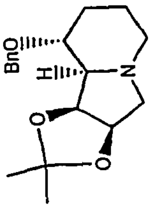


(III-21)





(III-22)



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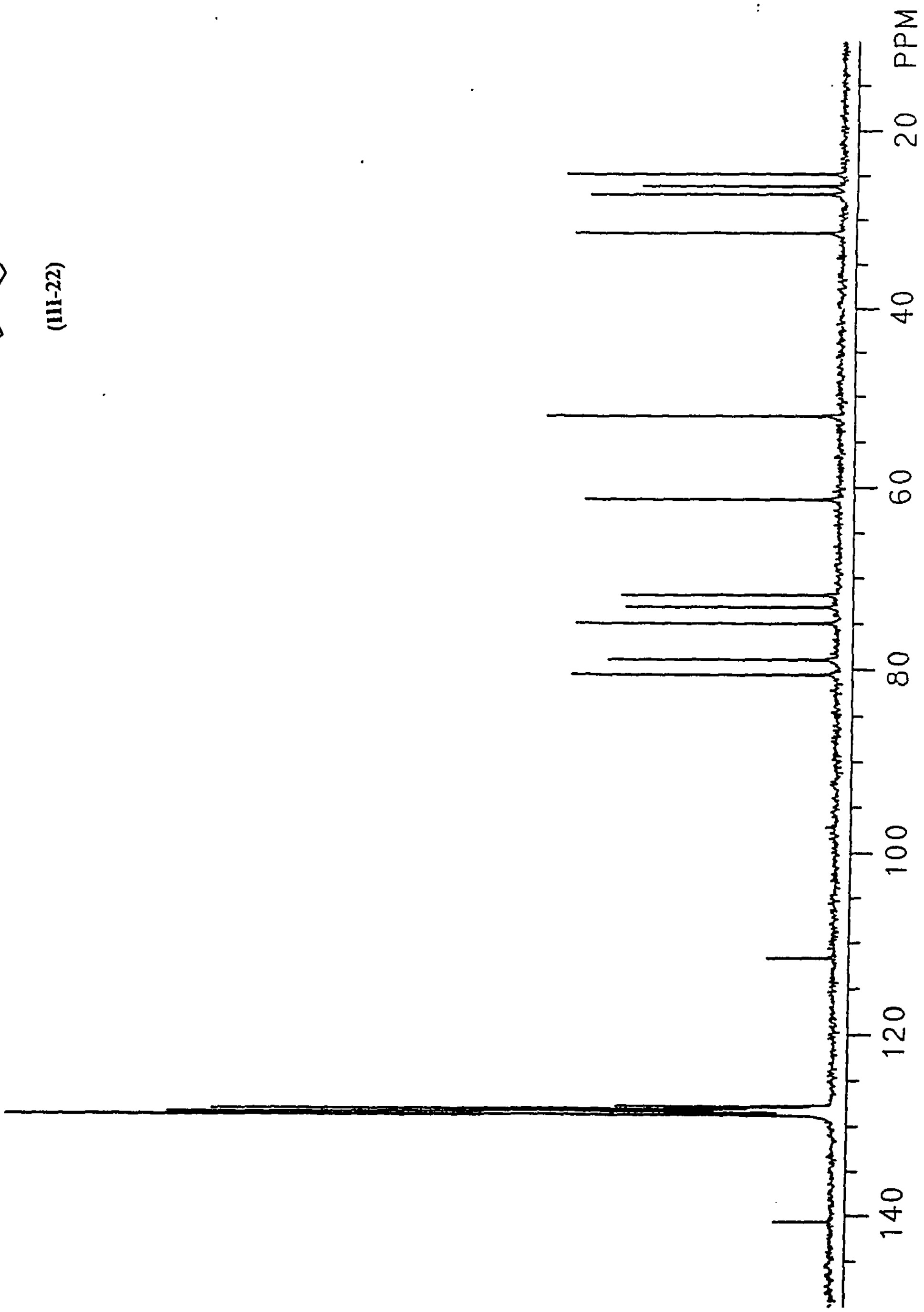
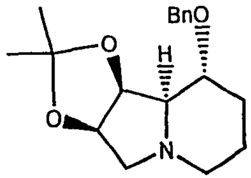
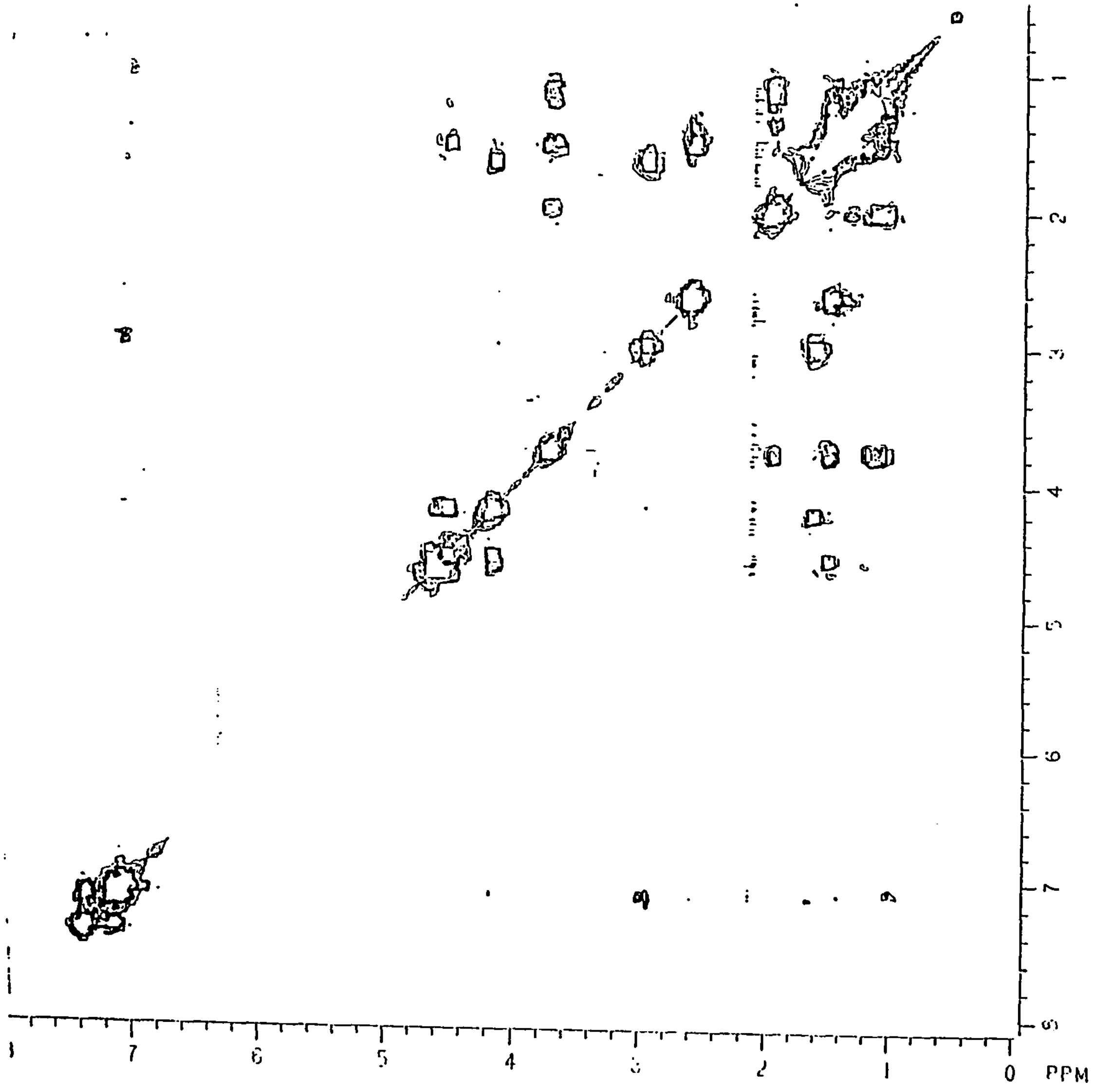
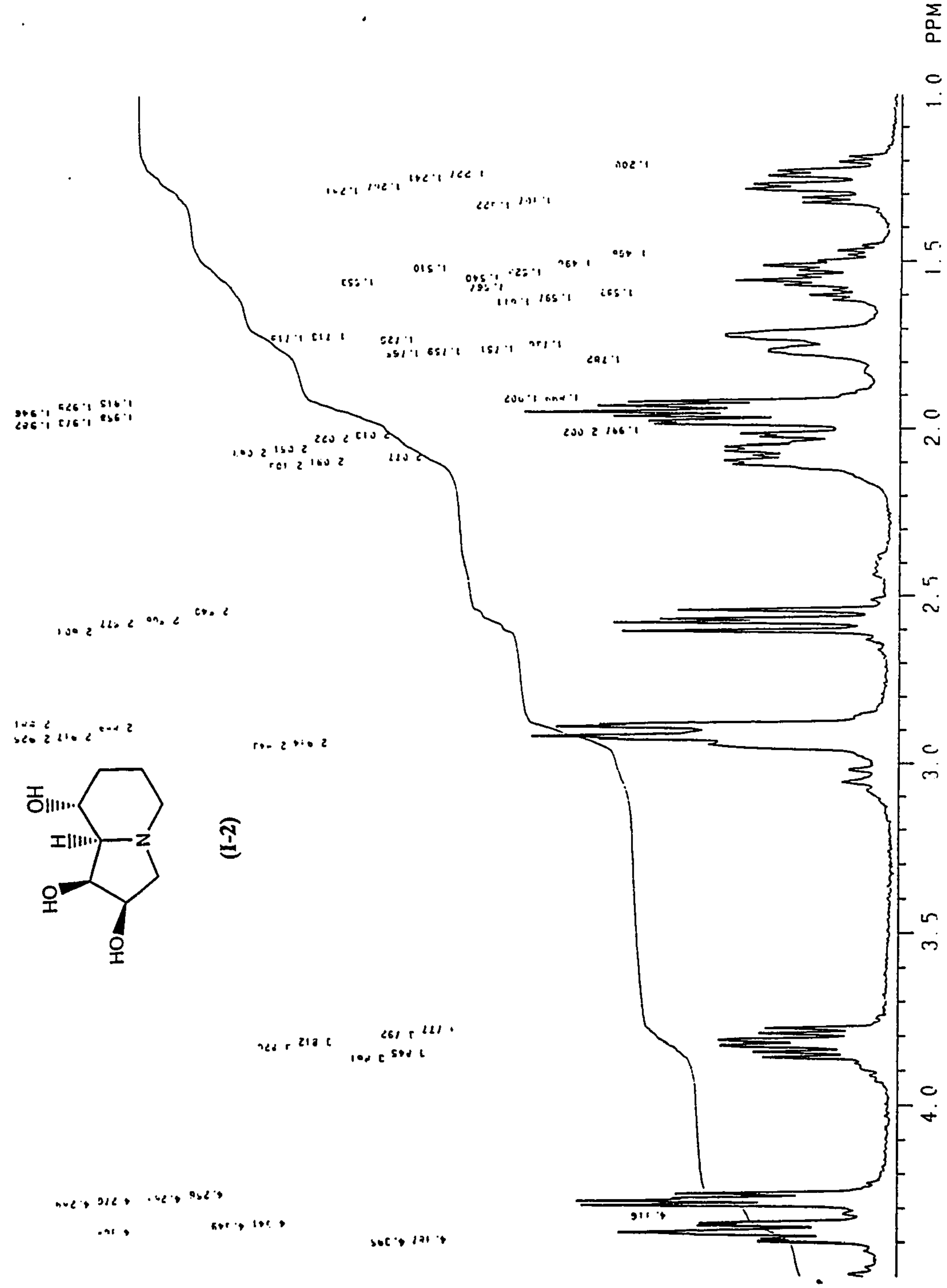


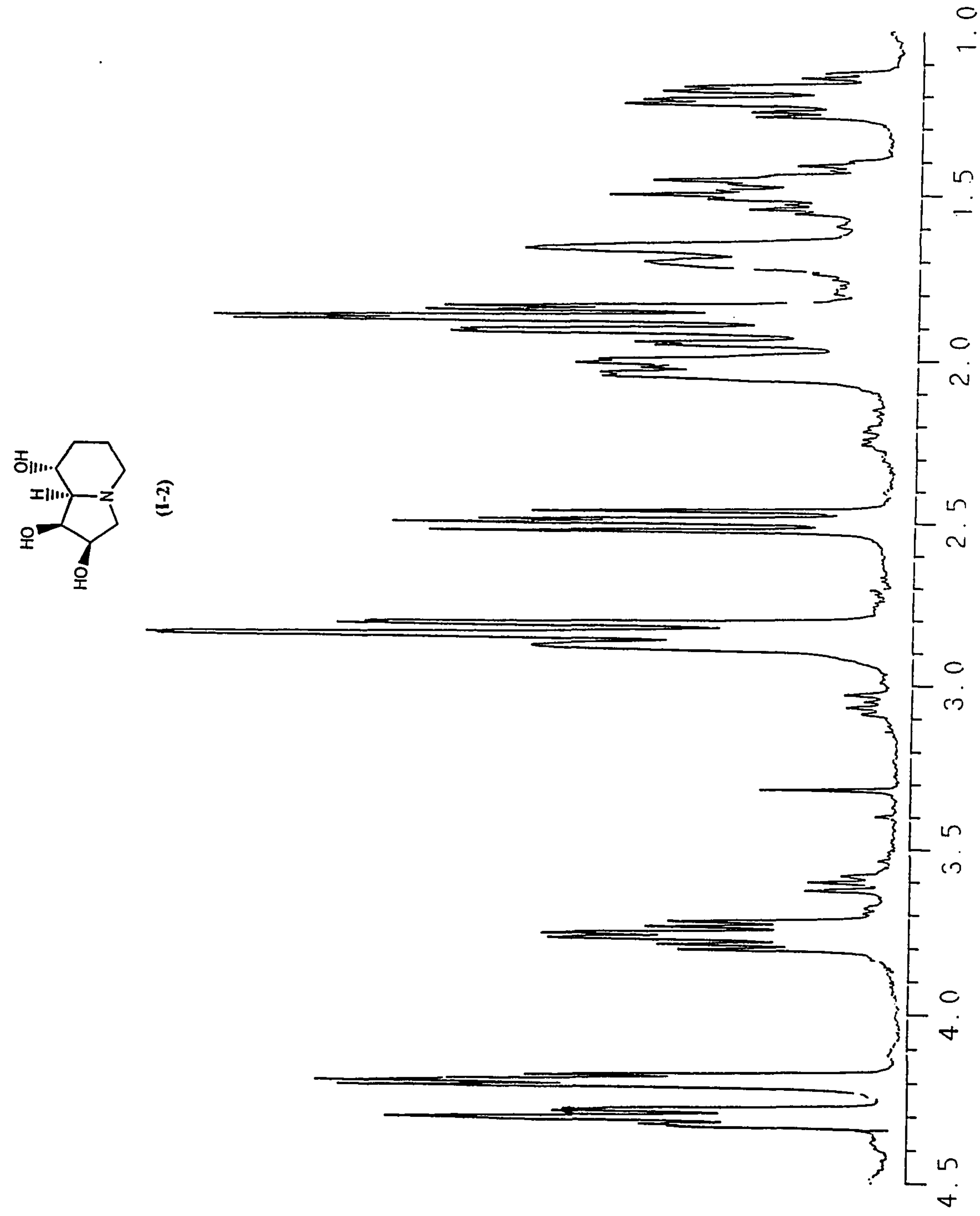


(III-22)

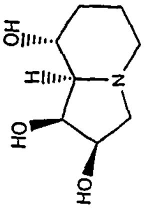




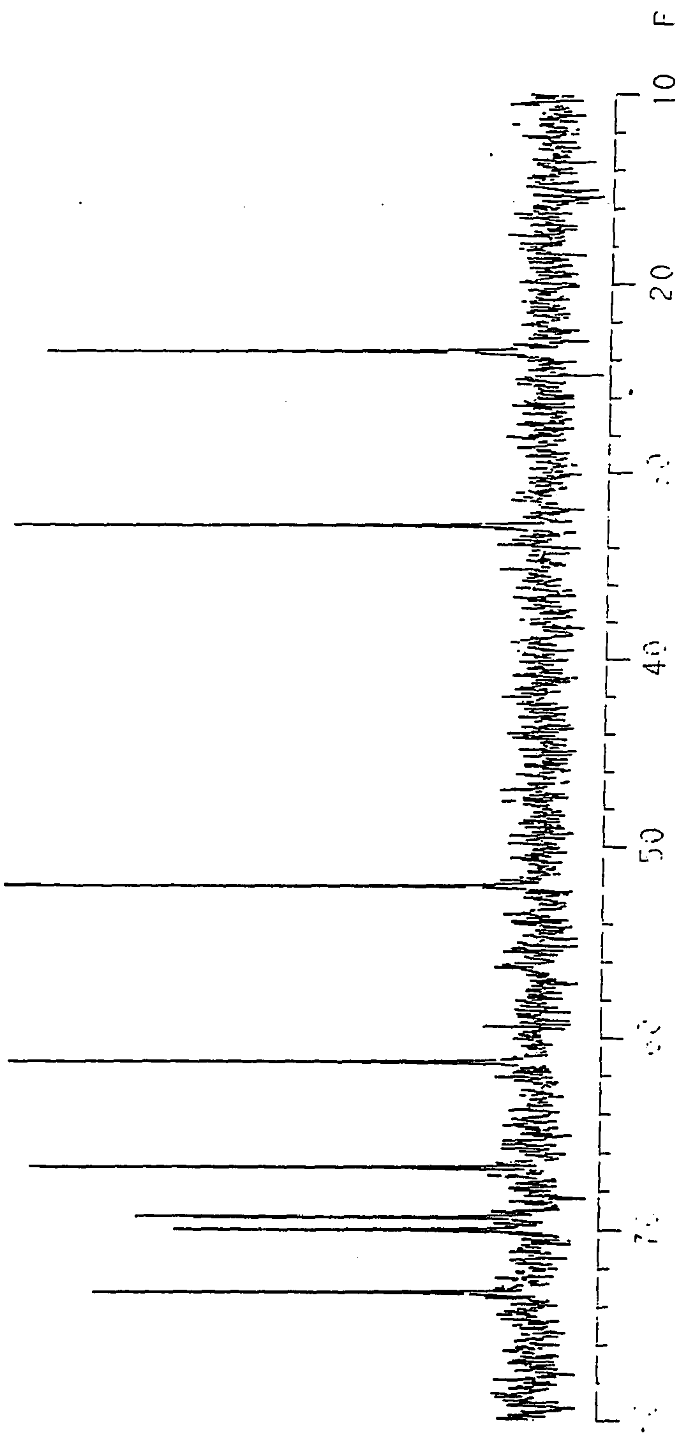
(I-2)

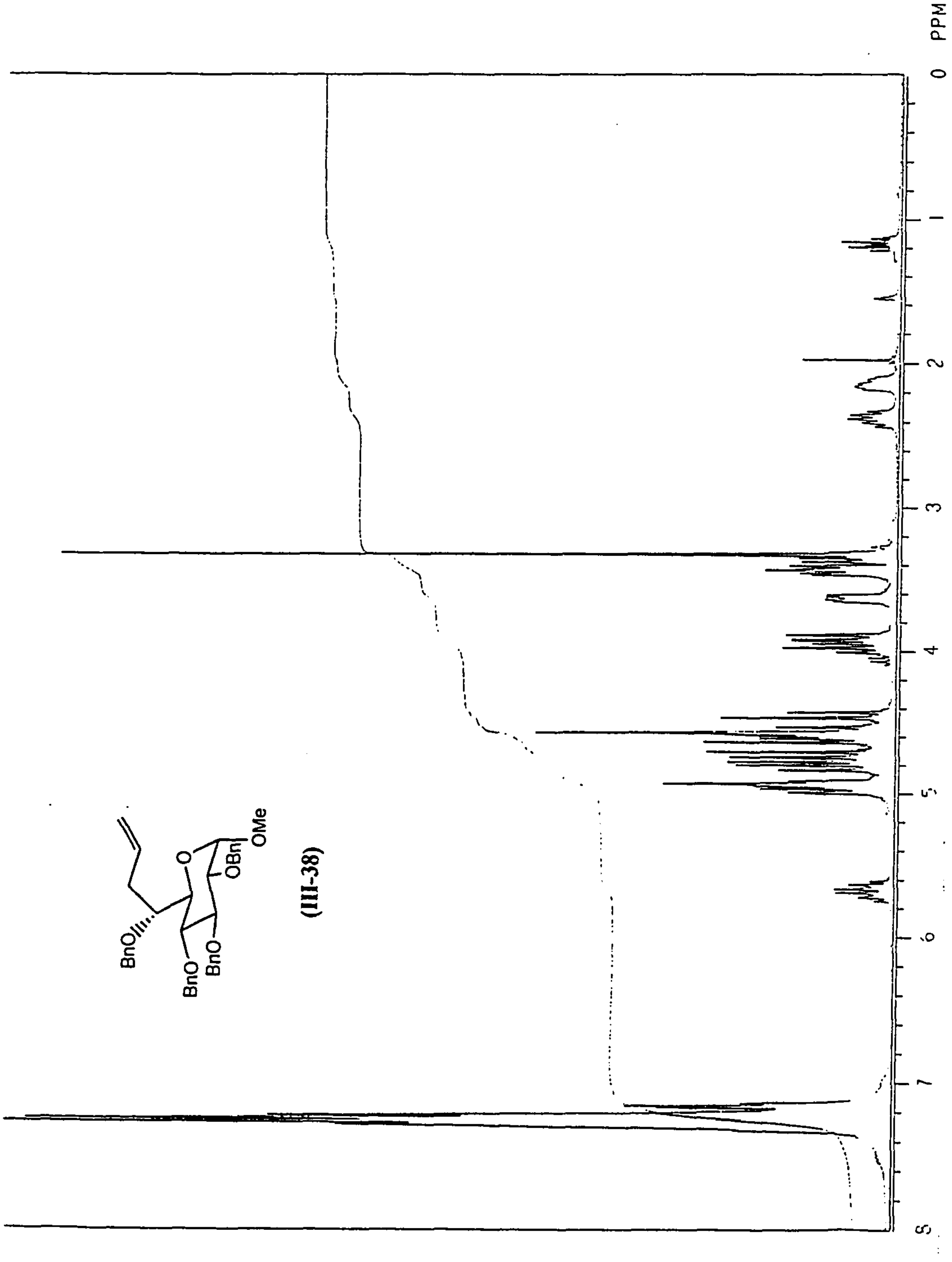


HO
HO
H
OH
N
(I-2)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

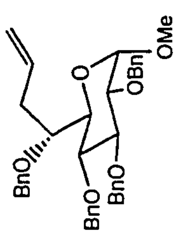


Swainsonine (I-2)

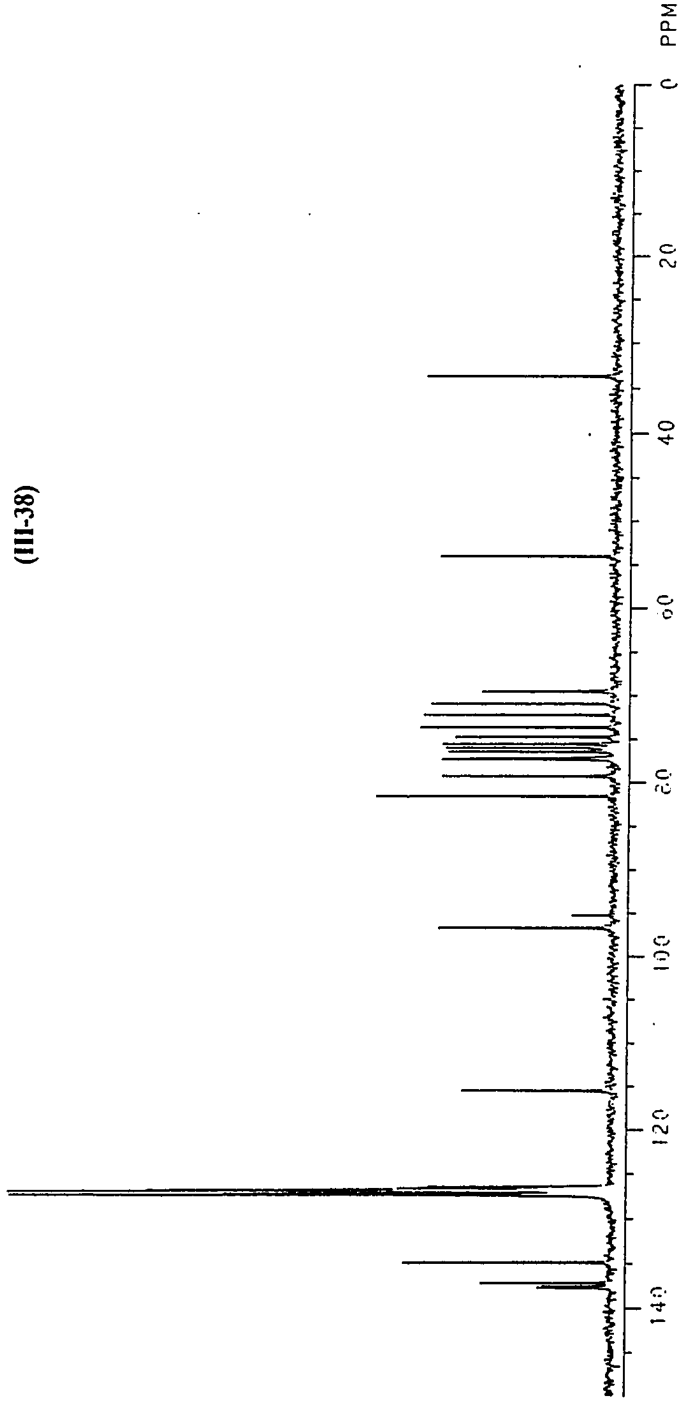


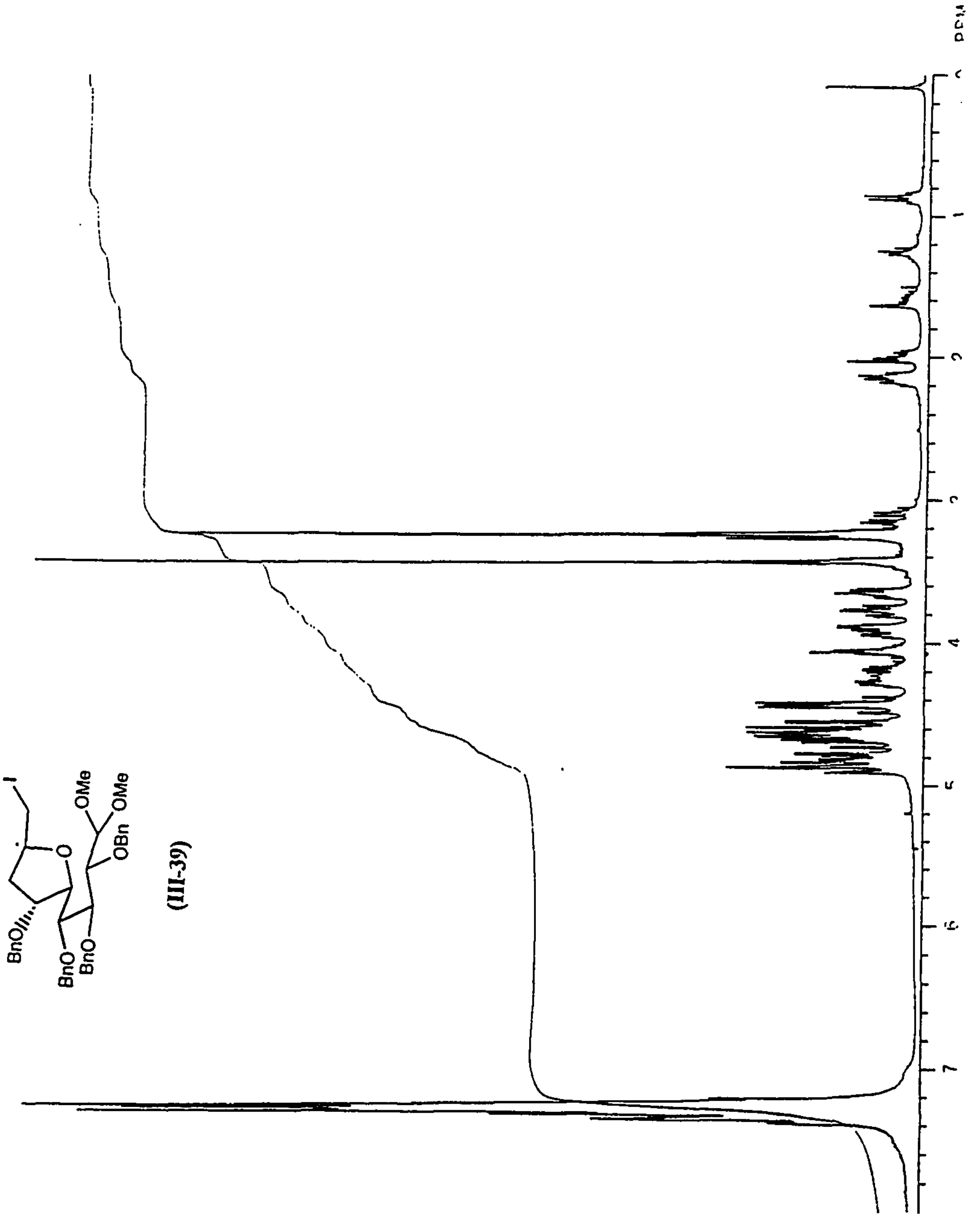


(III-38)

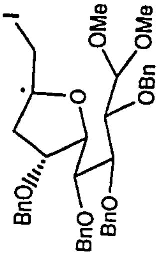


(III-38)

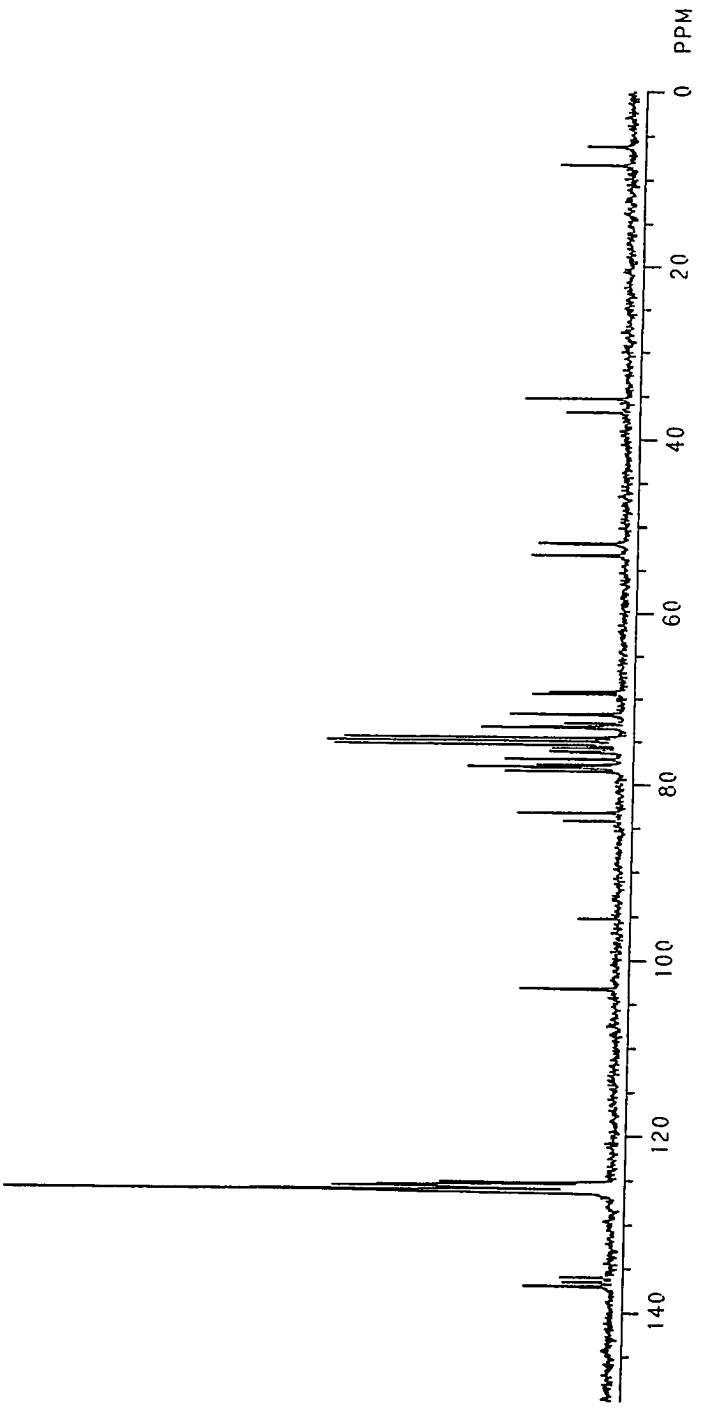


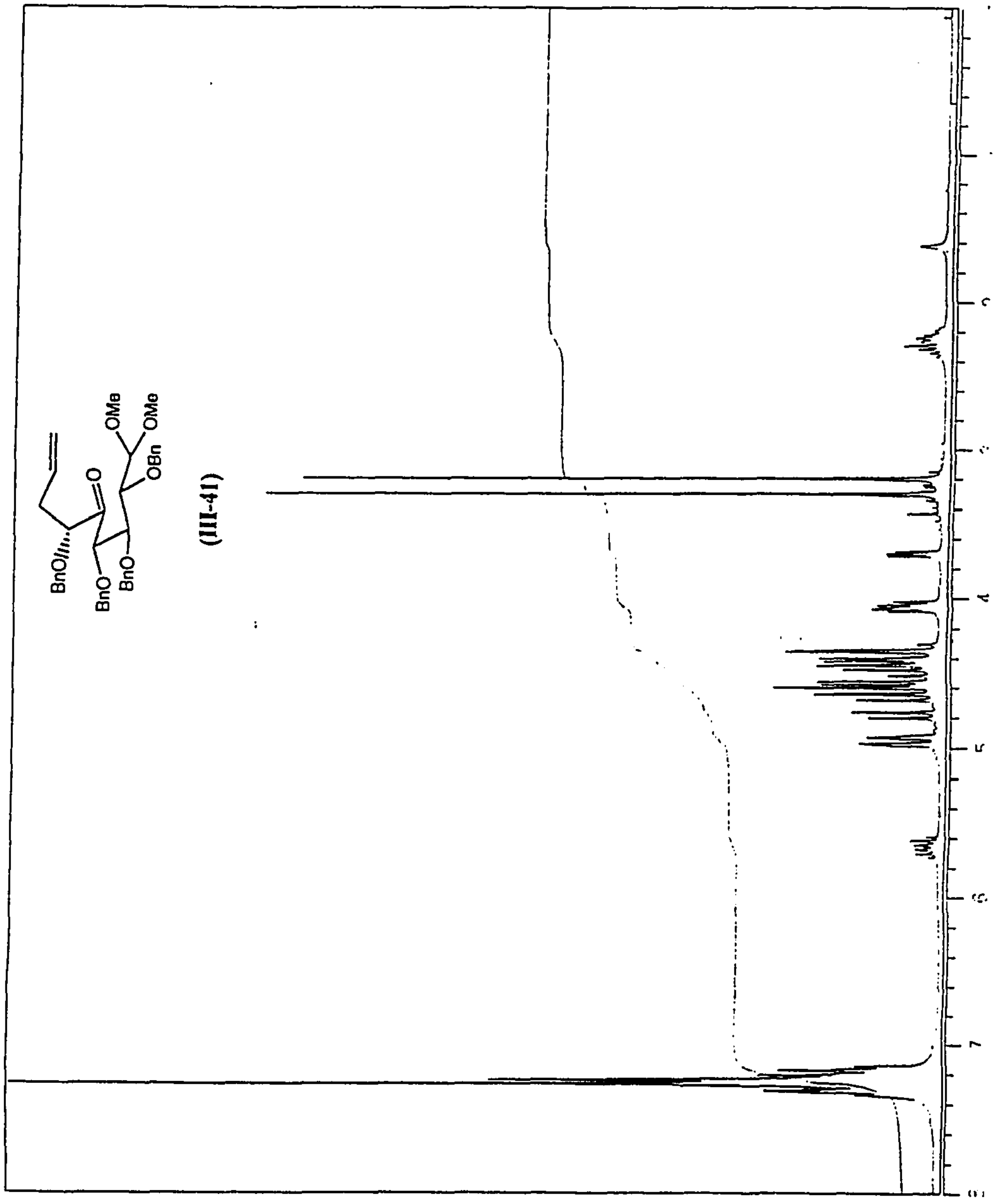


(III-39)

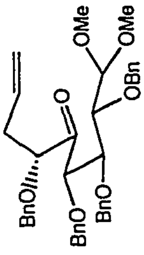


(III-39)

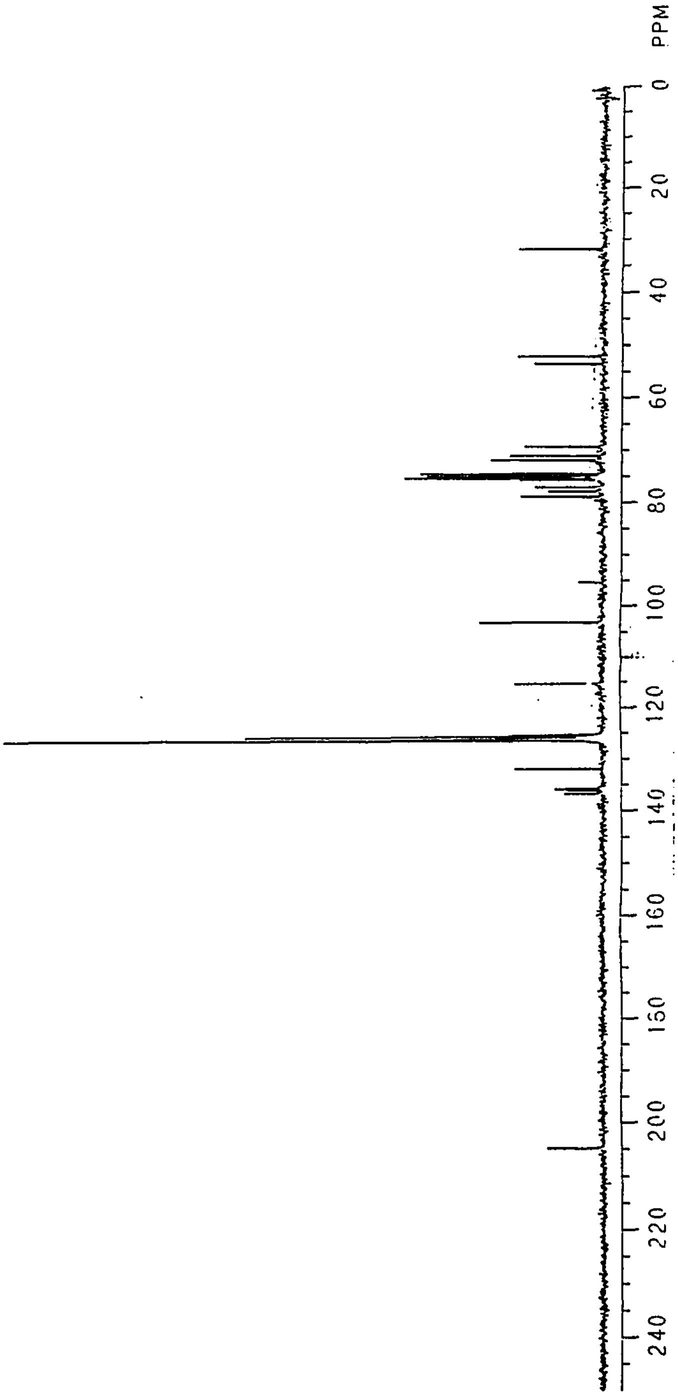


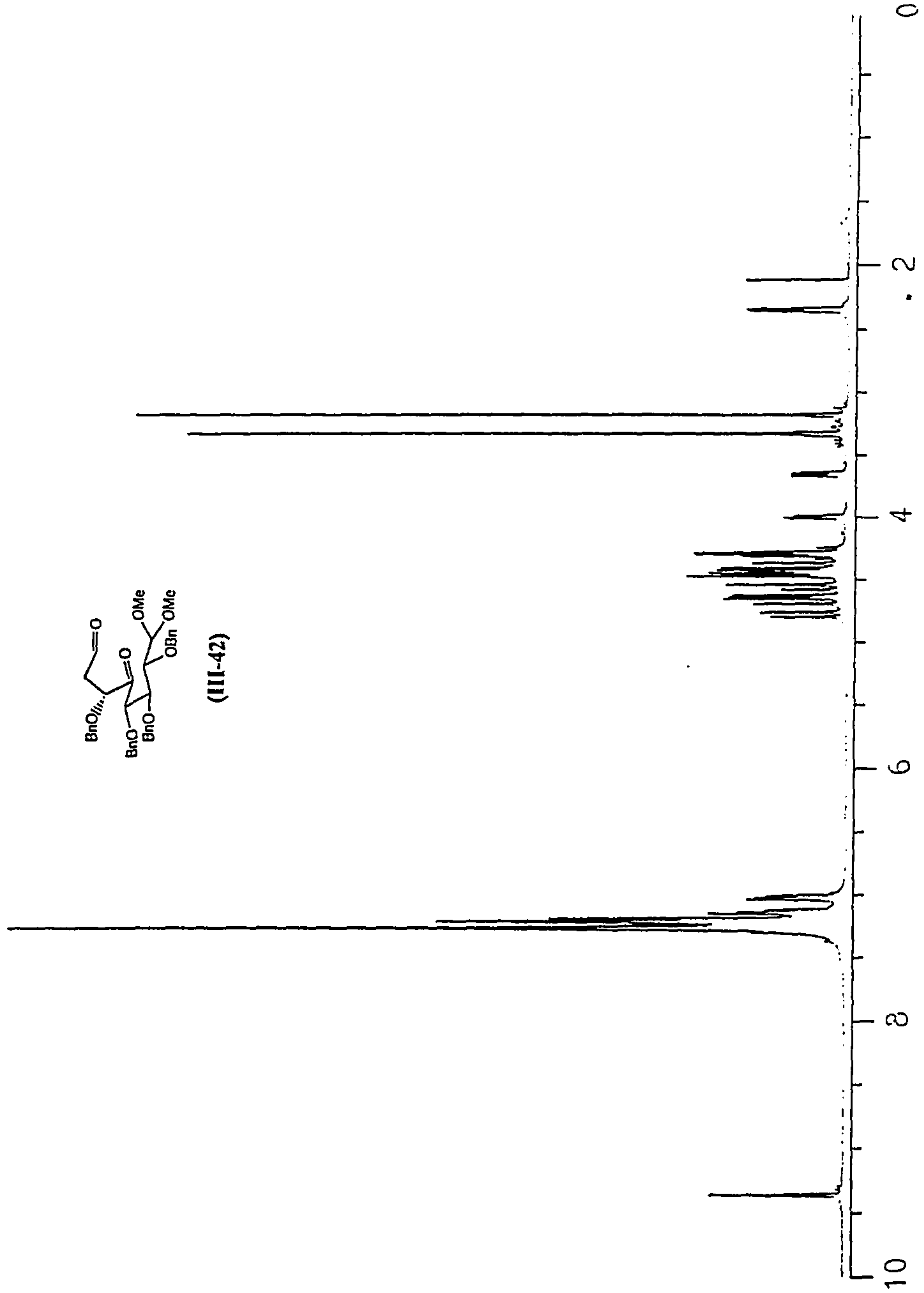


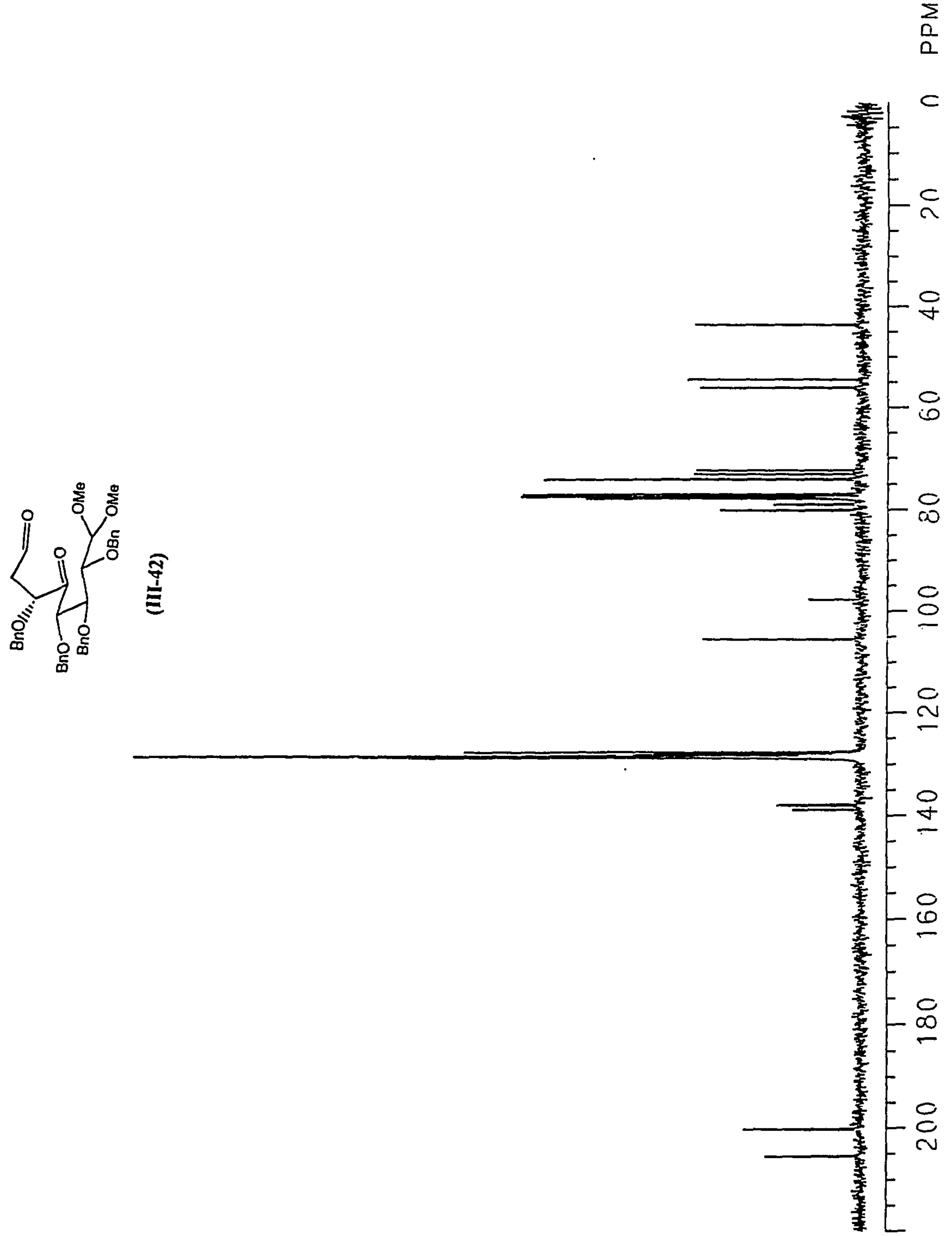
(III-41)


BnO
BnO
BnO
O
OMe
OMe
OBn

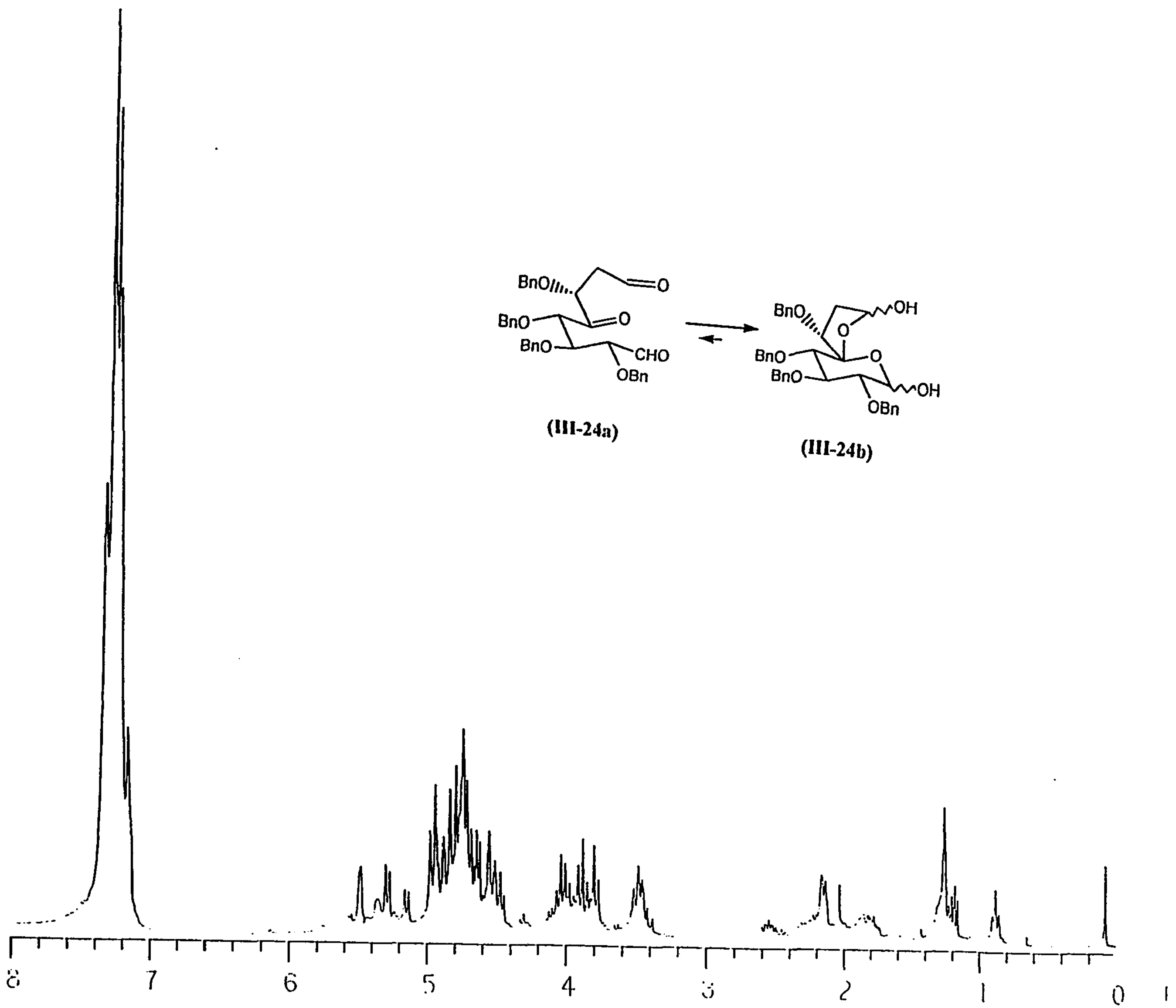
(III-41)


PPM
0
20
40
60
80
100
120
140
160
180
200
220
240


(III-42)

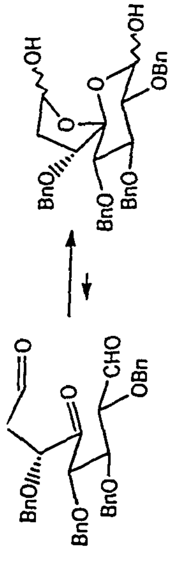

BnO
BnO
BnO
O
O
OBn
OMe
OMe
PPM
0
20
40
60
80
100
120
140
160
180
200

(III-42)



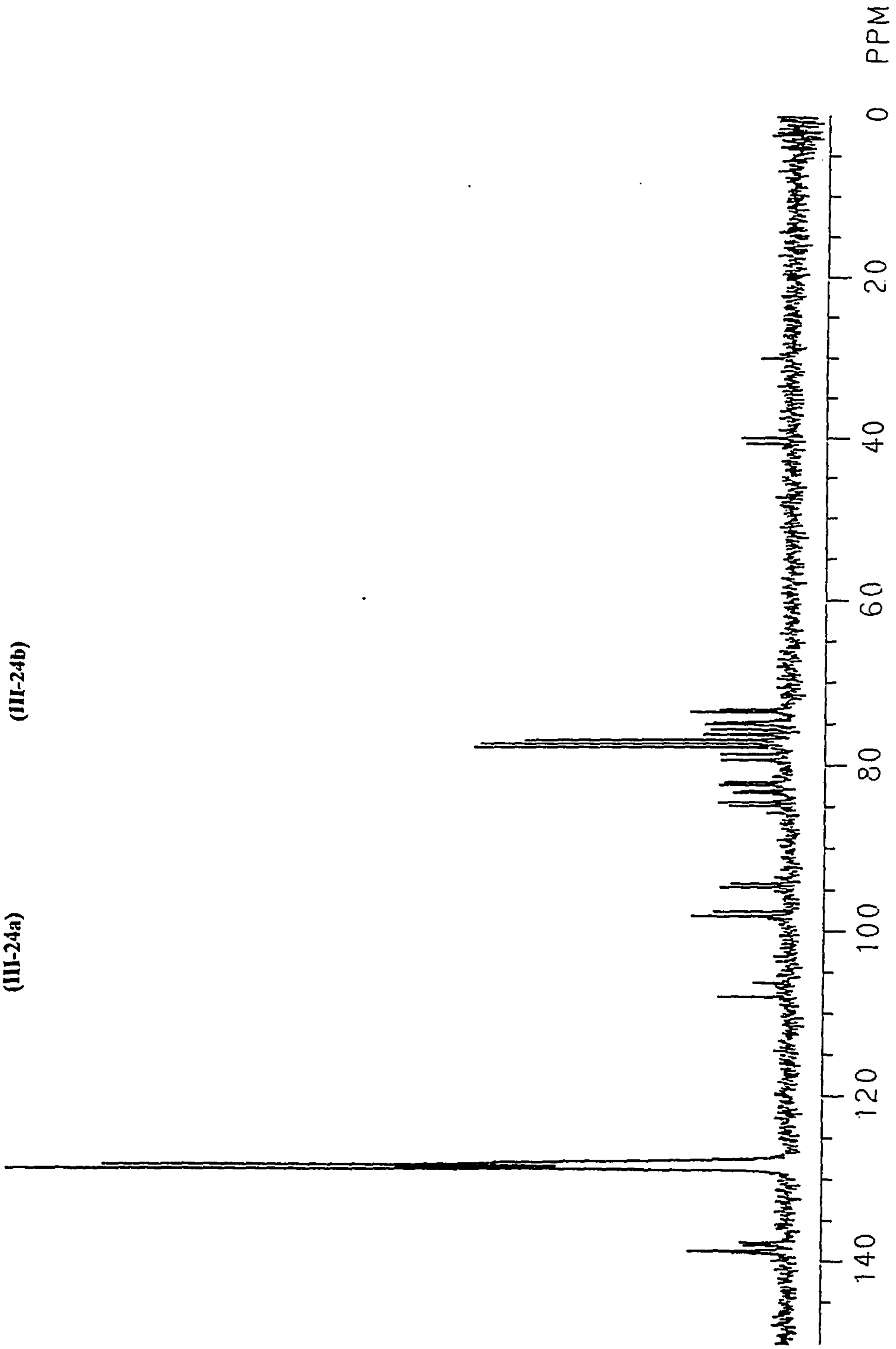
(III-24a)

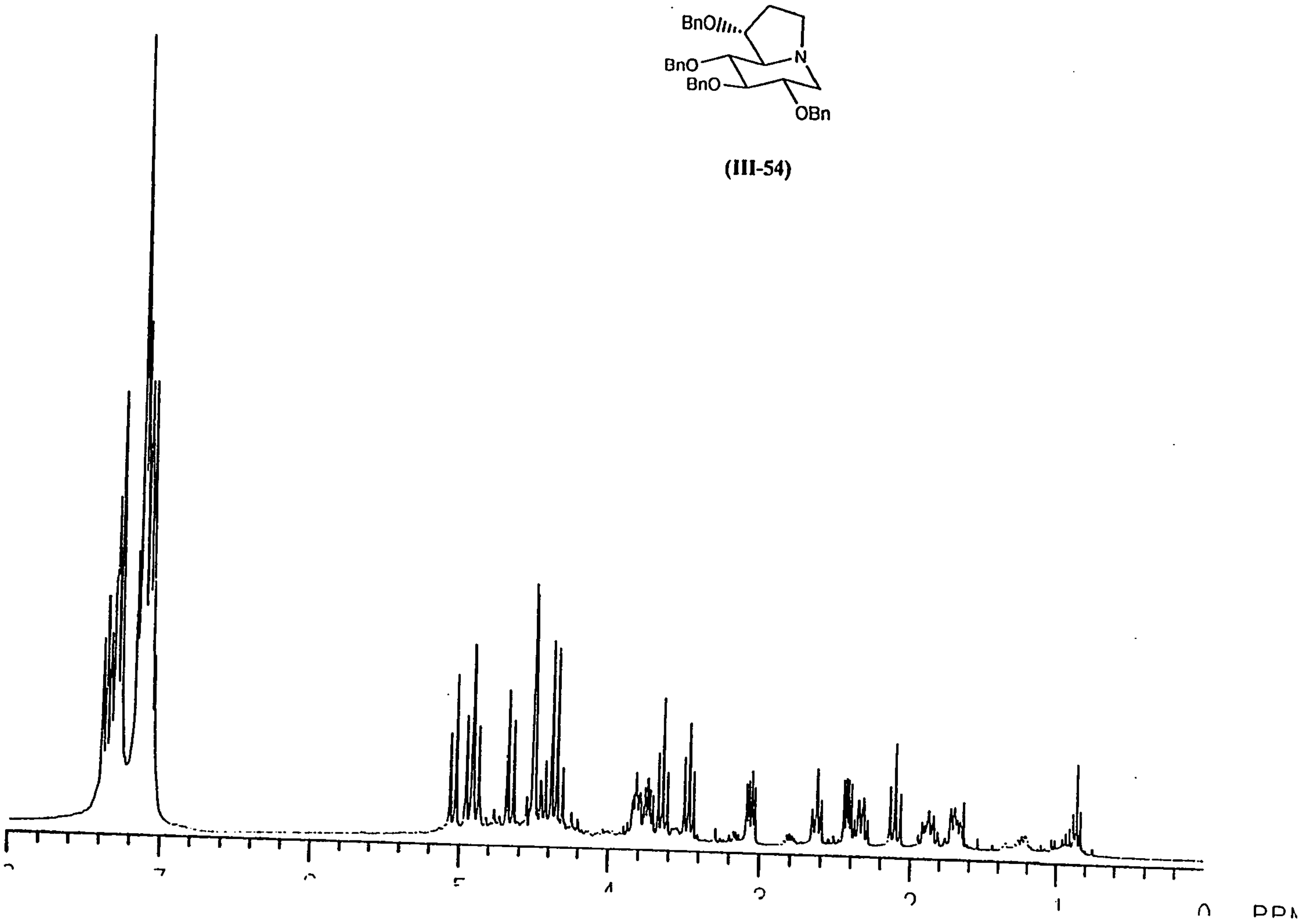
(III-24b)



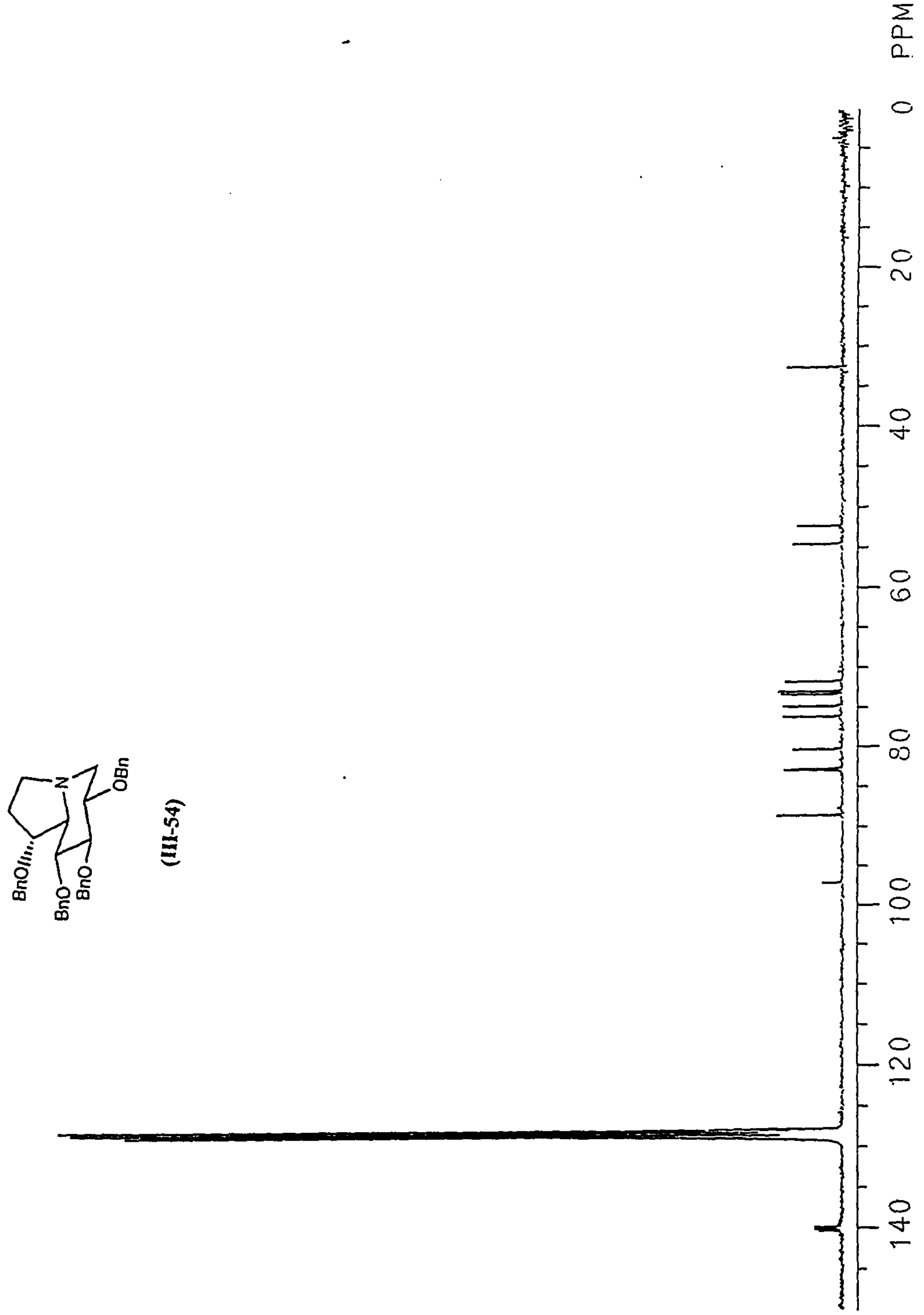
(III-24a)

(III-24b)

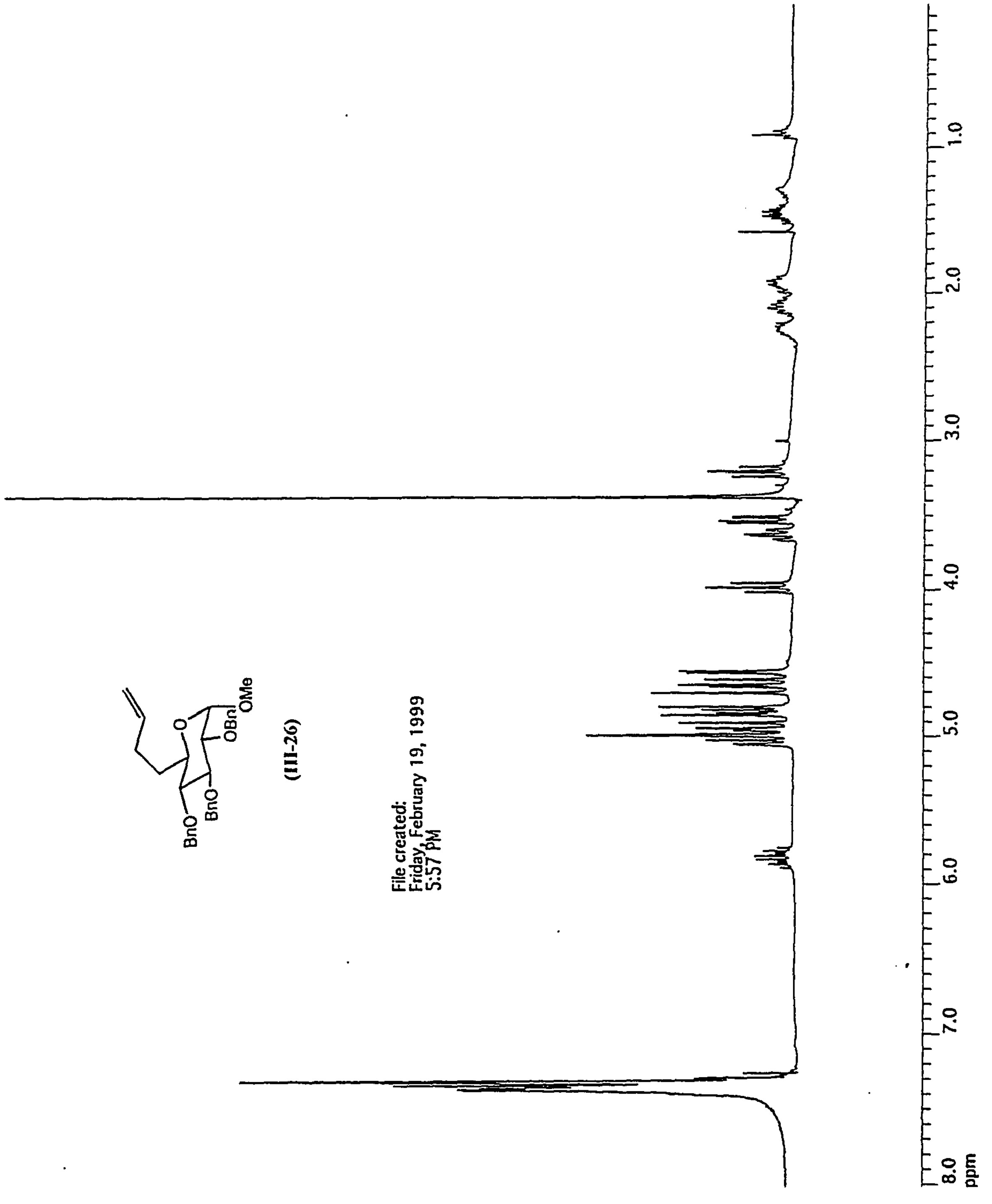




(III-54)

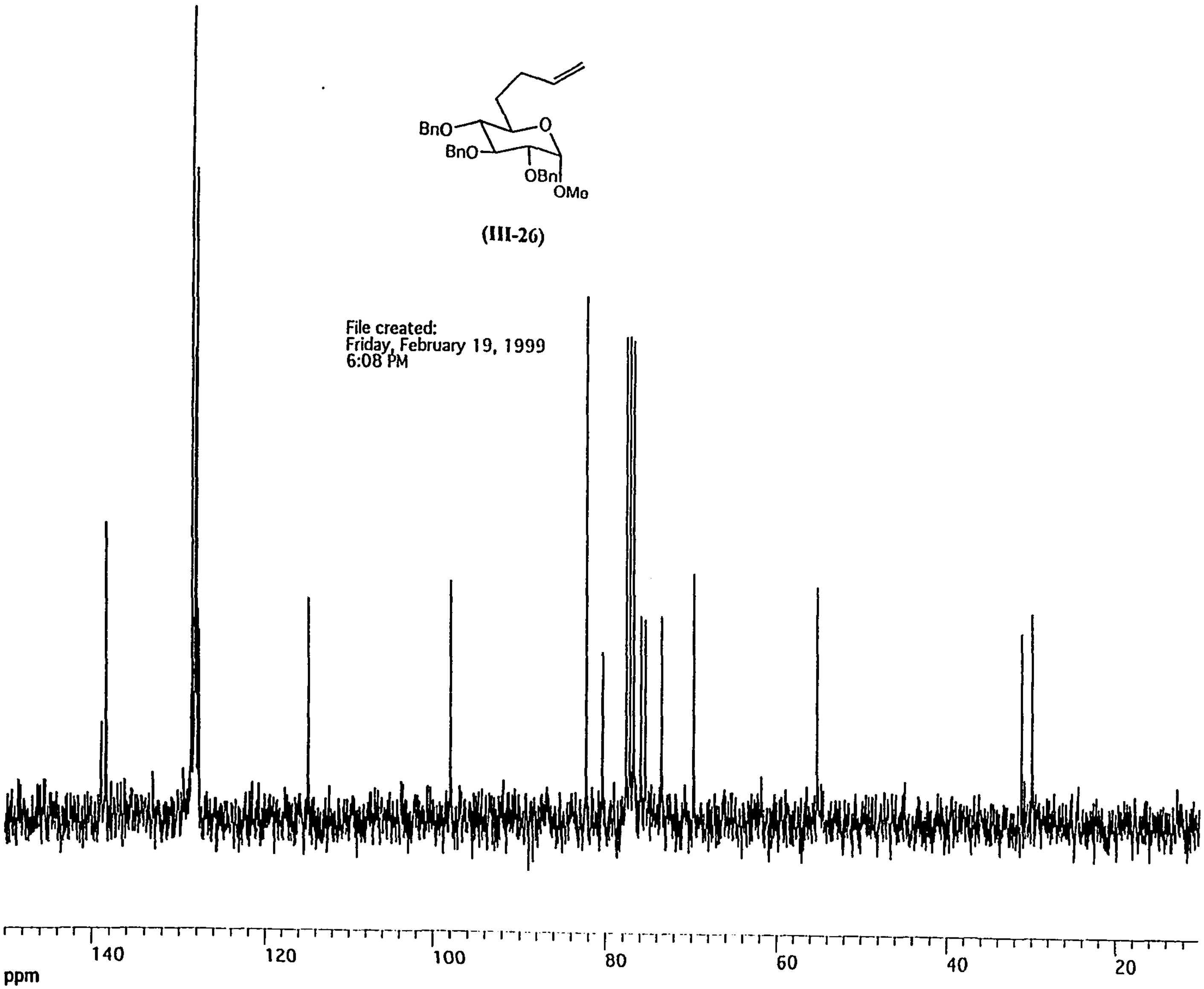


(III-54)



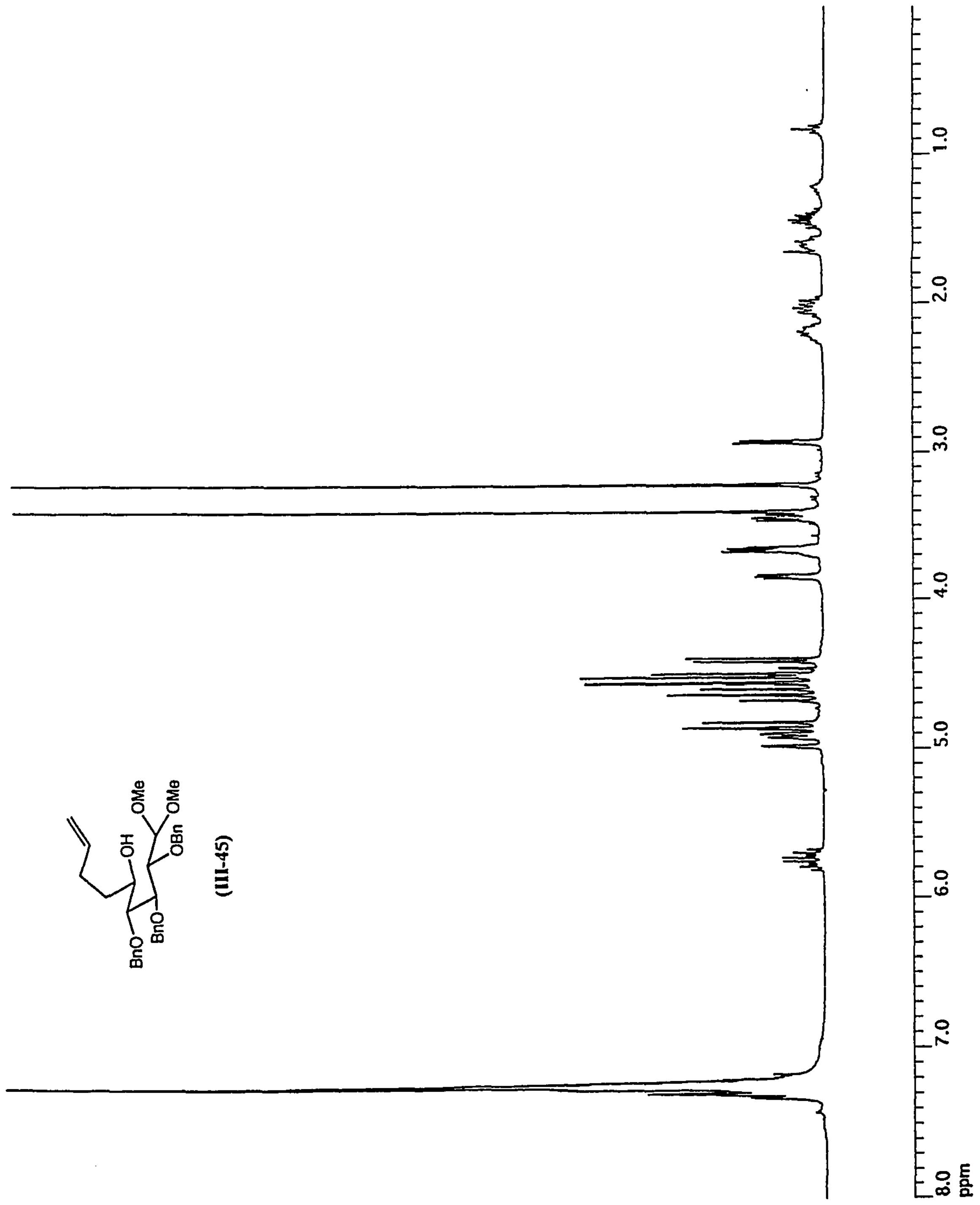
(III-26)

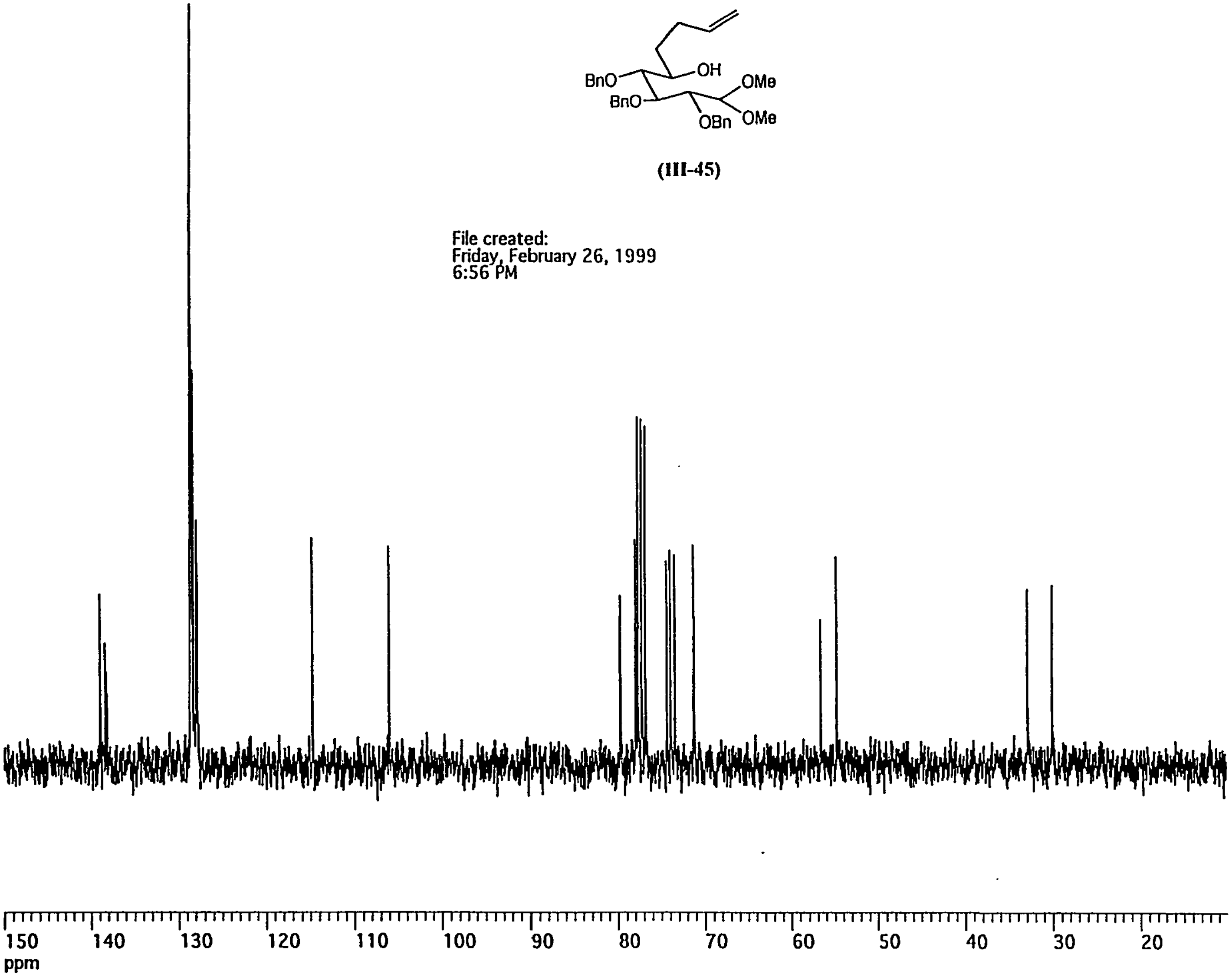
File created:
Friday, February 19, 1999
5:57 PM



(III-26)

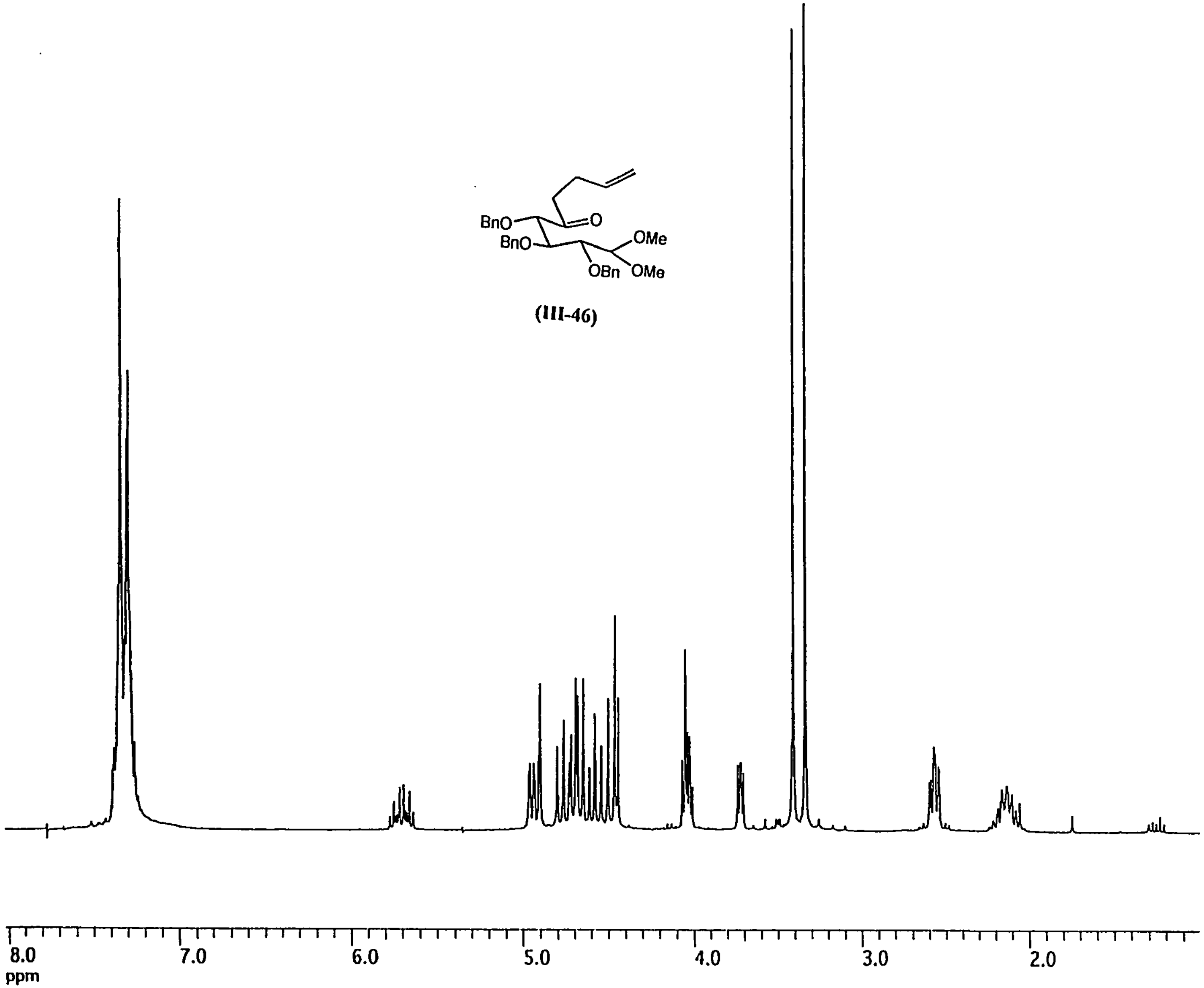
File created:
Friday, February 19, 1999
6:08 PM


(III-45)

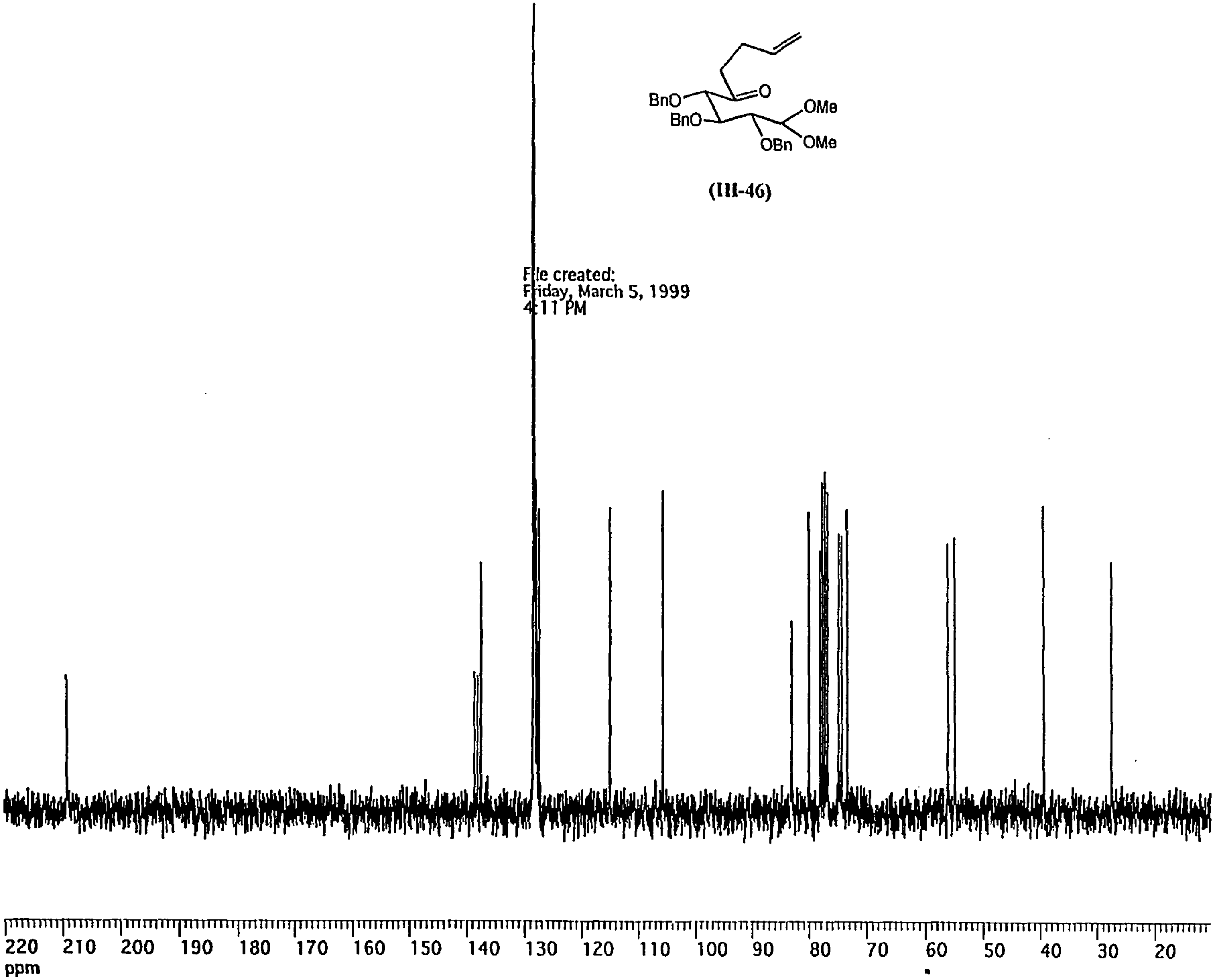


(III-45)

File created:
Friday, February 26, 1999
6:56 PM

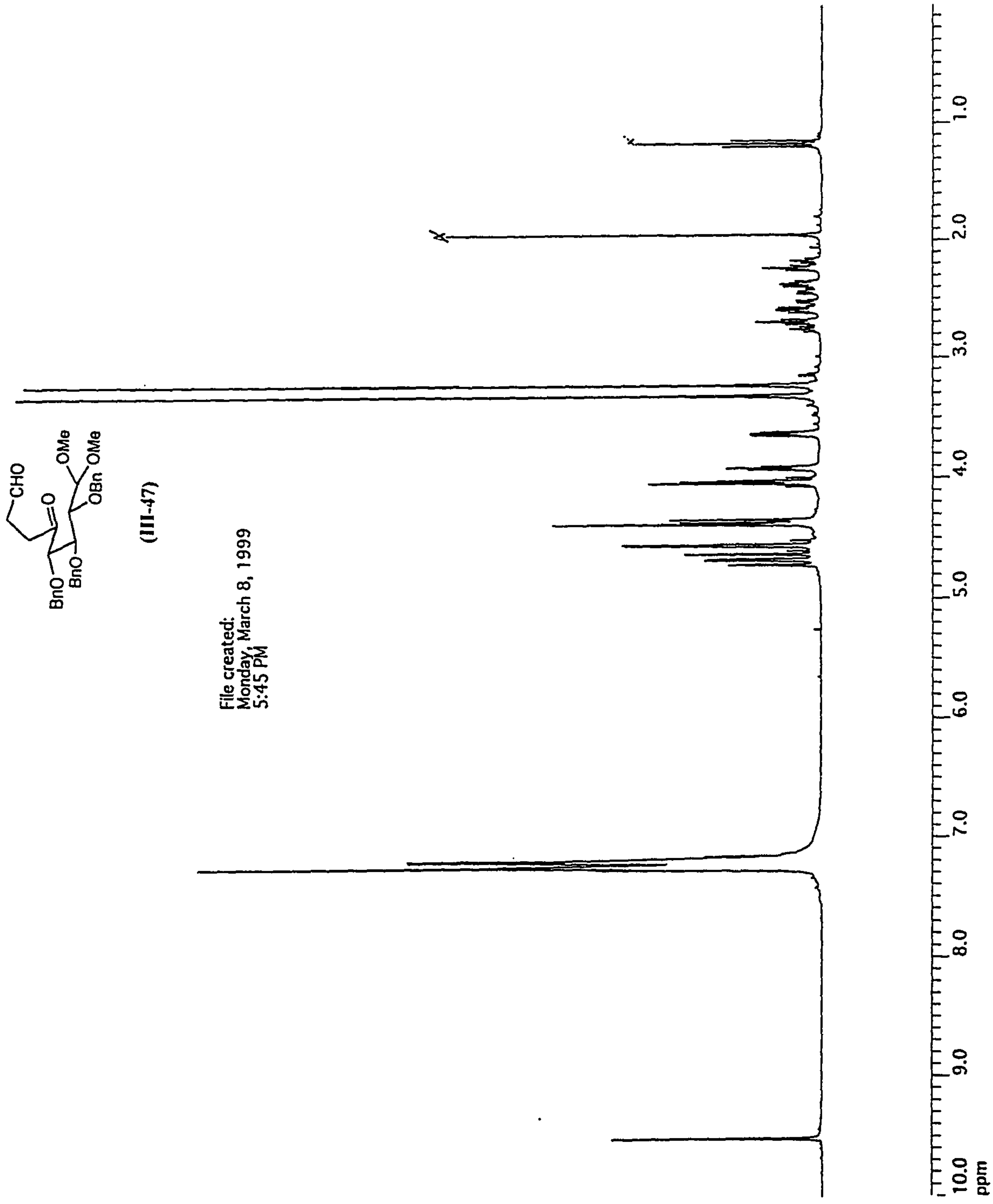


(III-46)



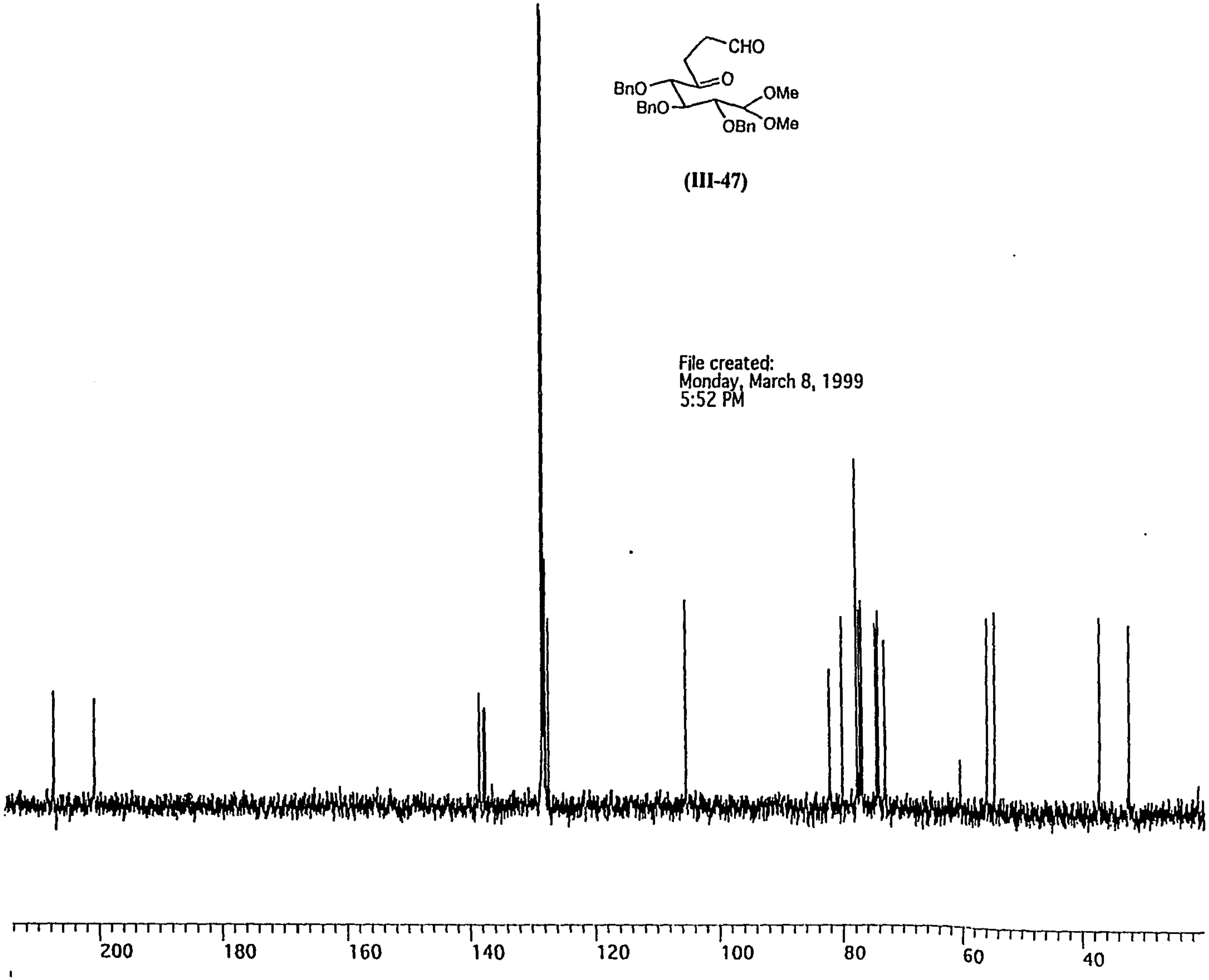
(III-46)

File created:
Friday, March 5, 1999
4:11 PM



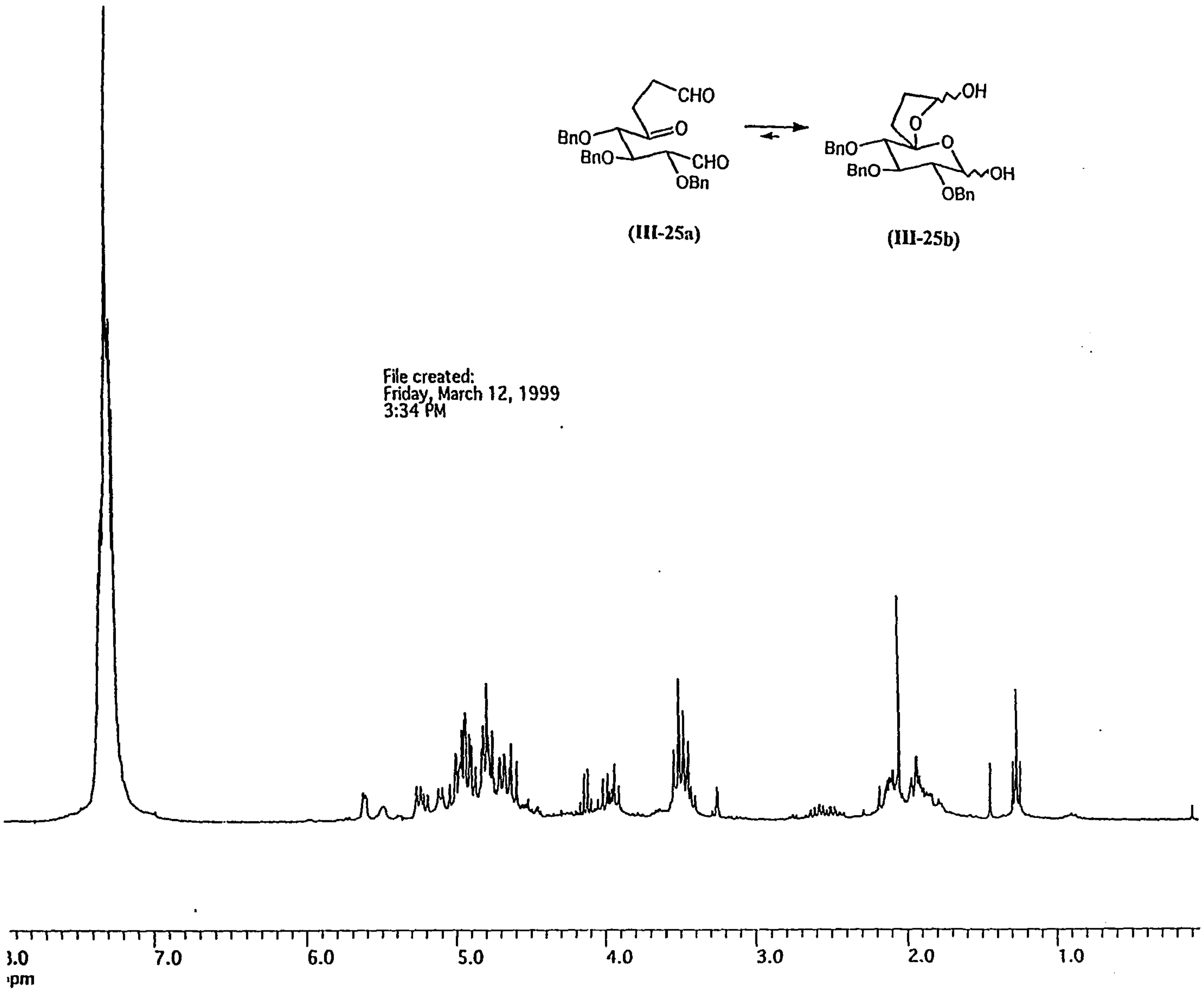
(III-47)

File created:
Monday, March 8, 1999
5:45 PM



(III-47)

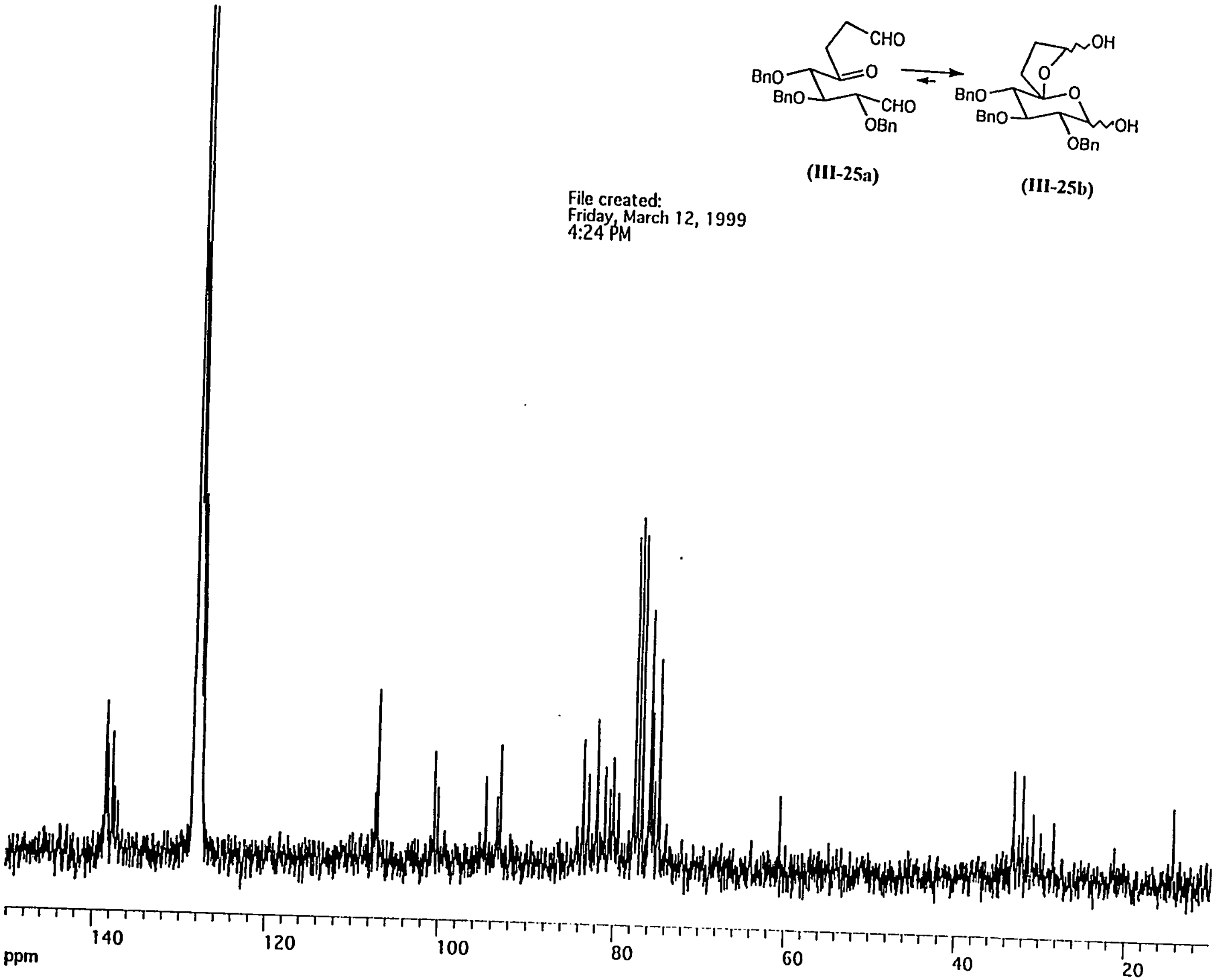
File created:
Monday, March 8, 1999
5:52 PM



(III-25a)

(III-25b)

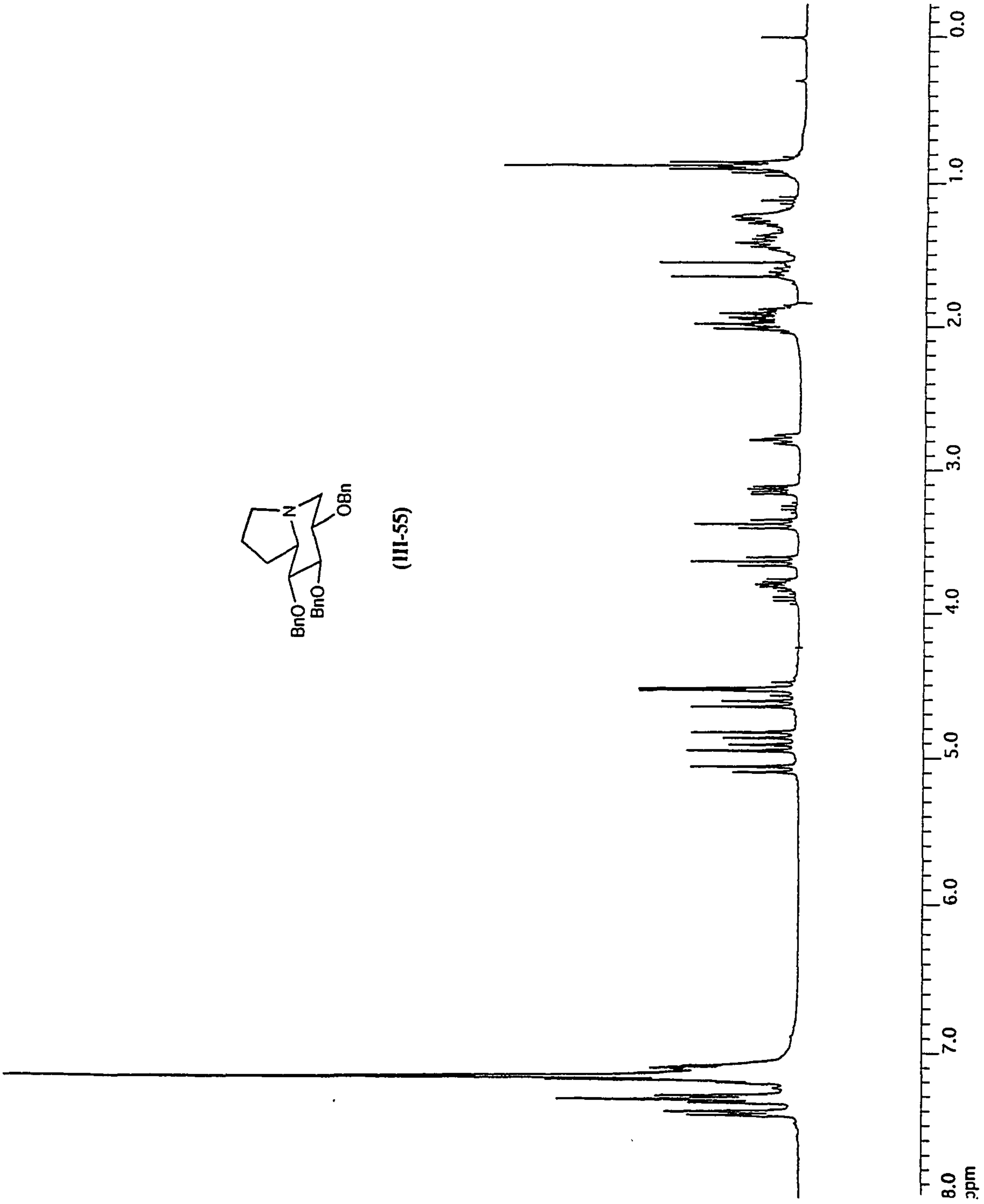
File created:
Friday, March 12, 1999
3:34 PM



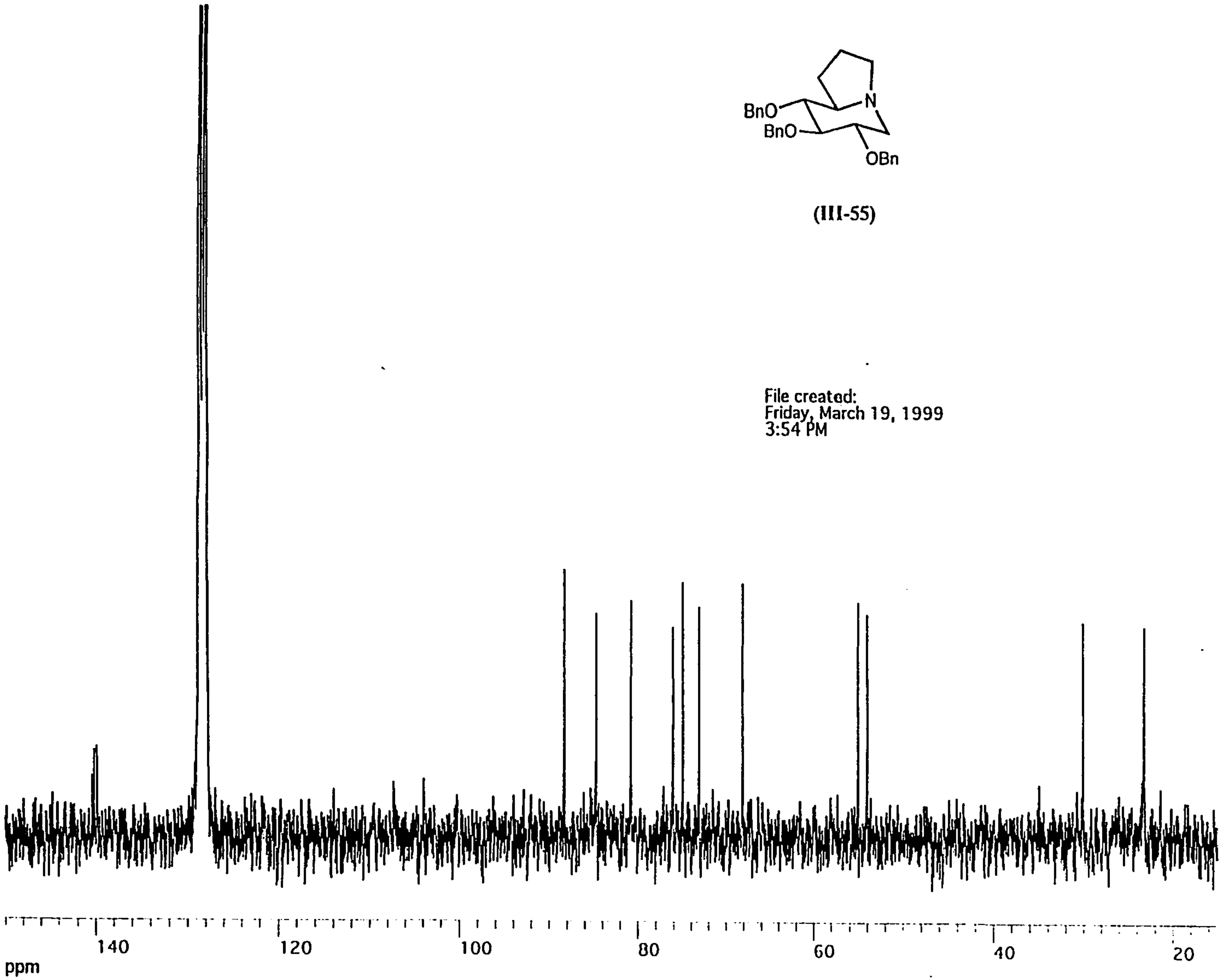
(III-25a)

(III-25b)

File created:
Friday, March 12, 1999
4:24 PM



(III-55)



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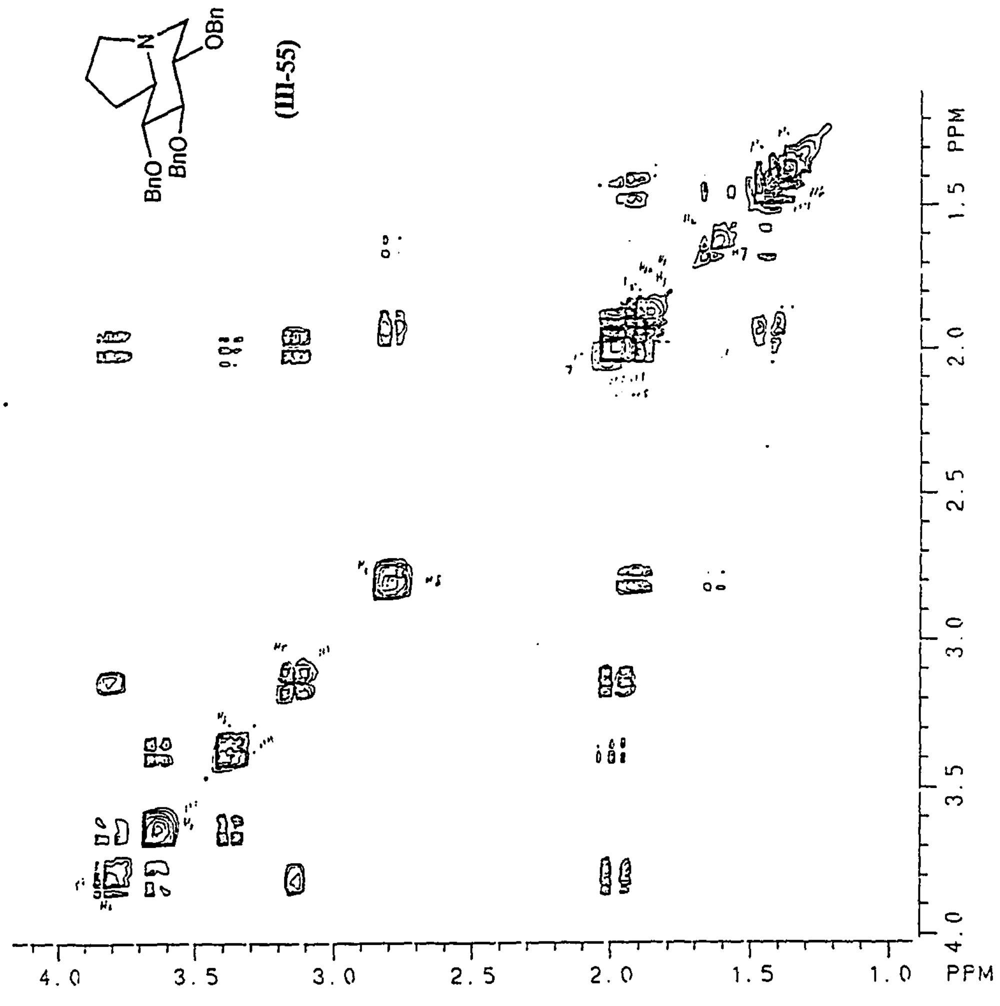
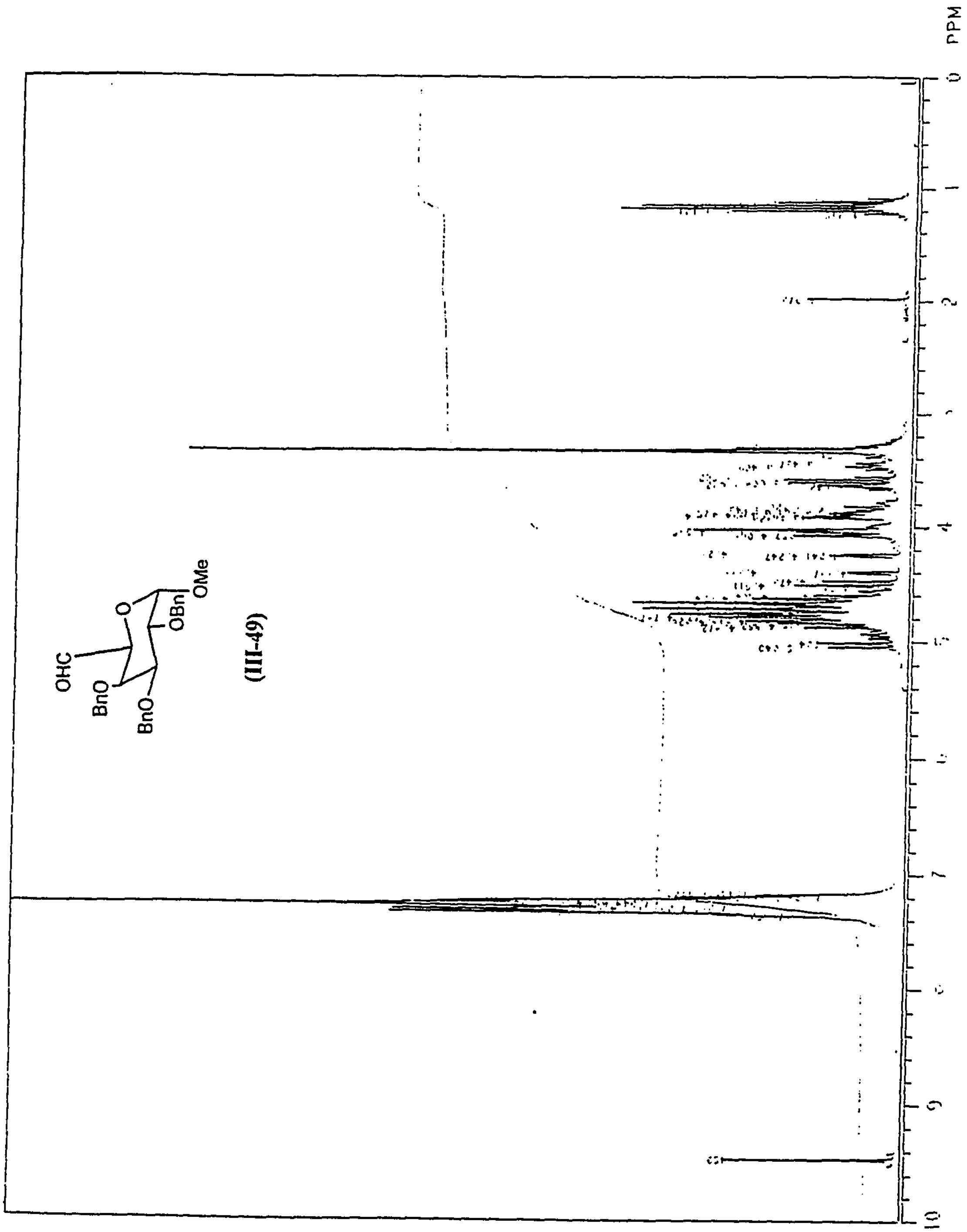
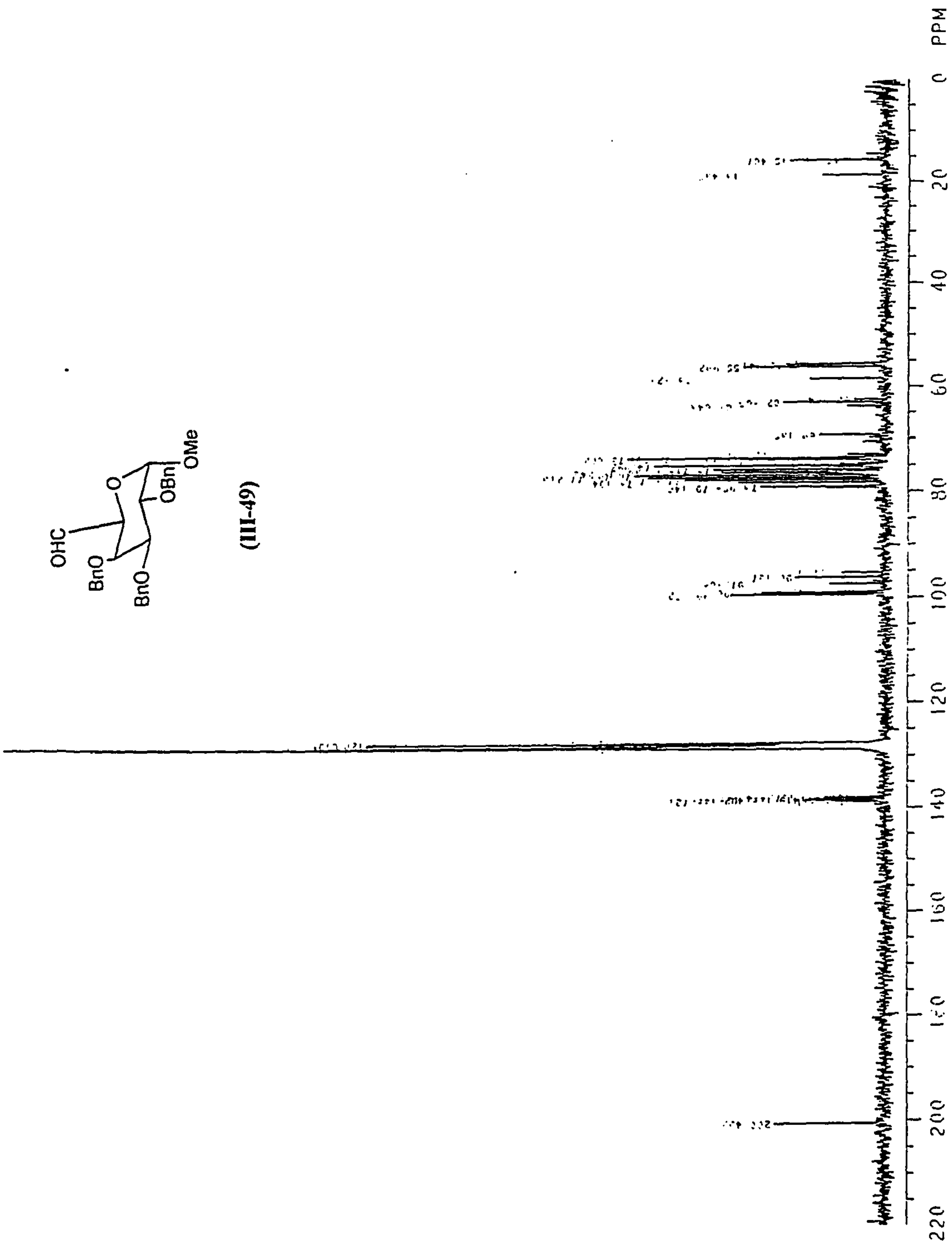


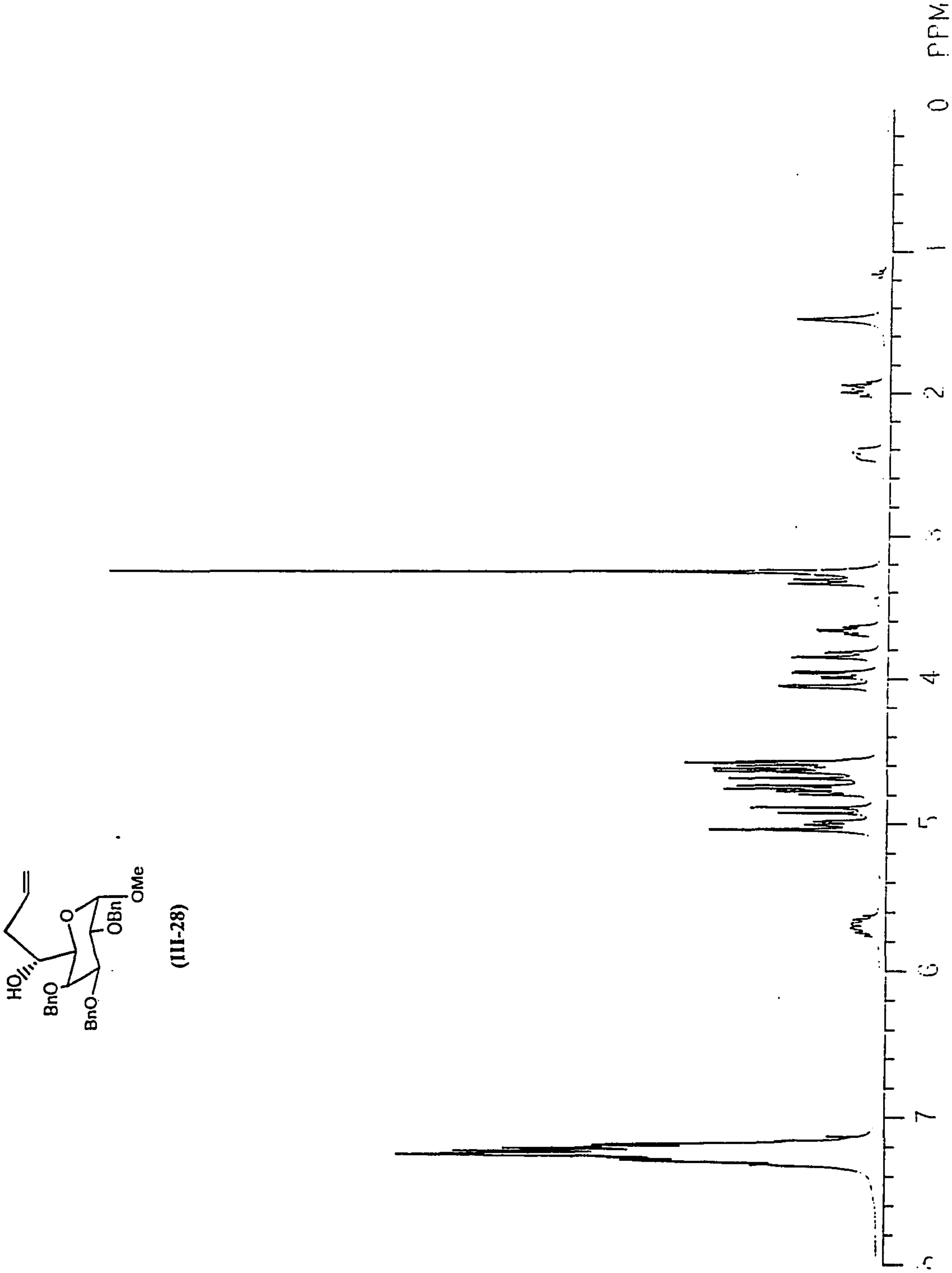
(III-55)



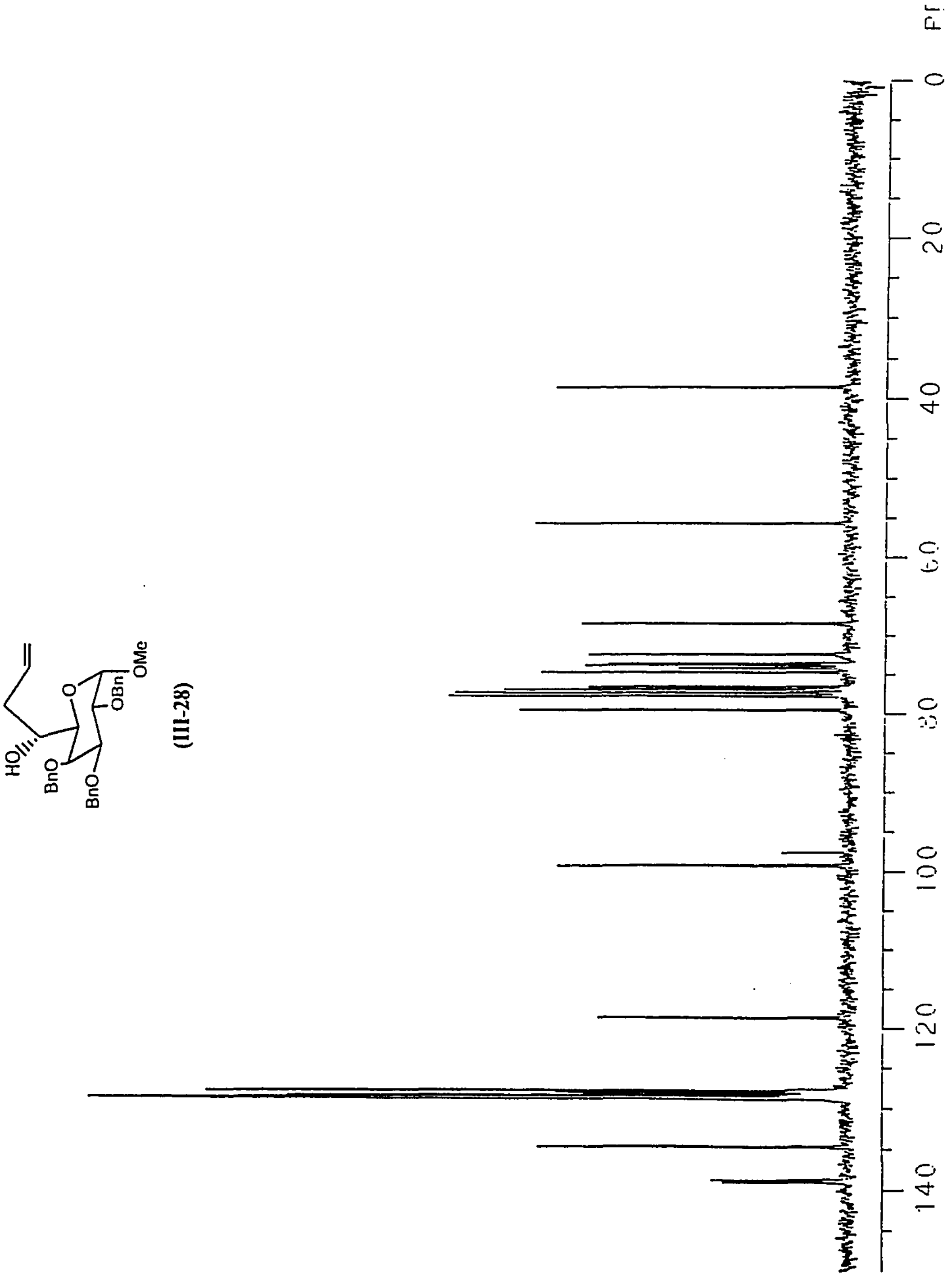
(III-49)



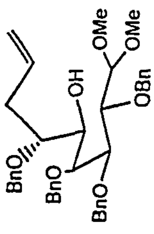
(III-49)



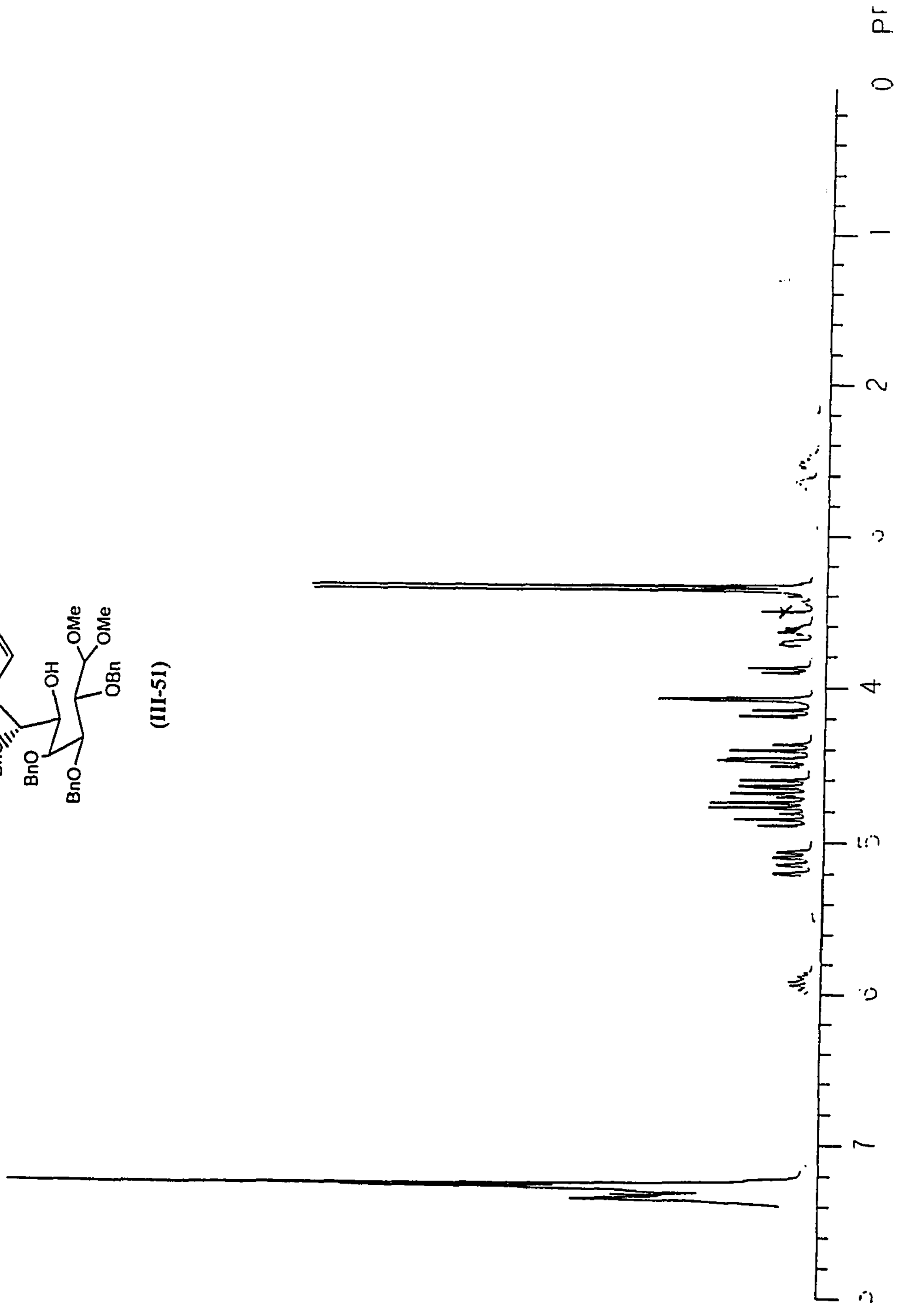
(III-28)

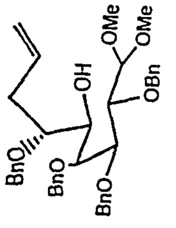


(III-28)

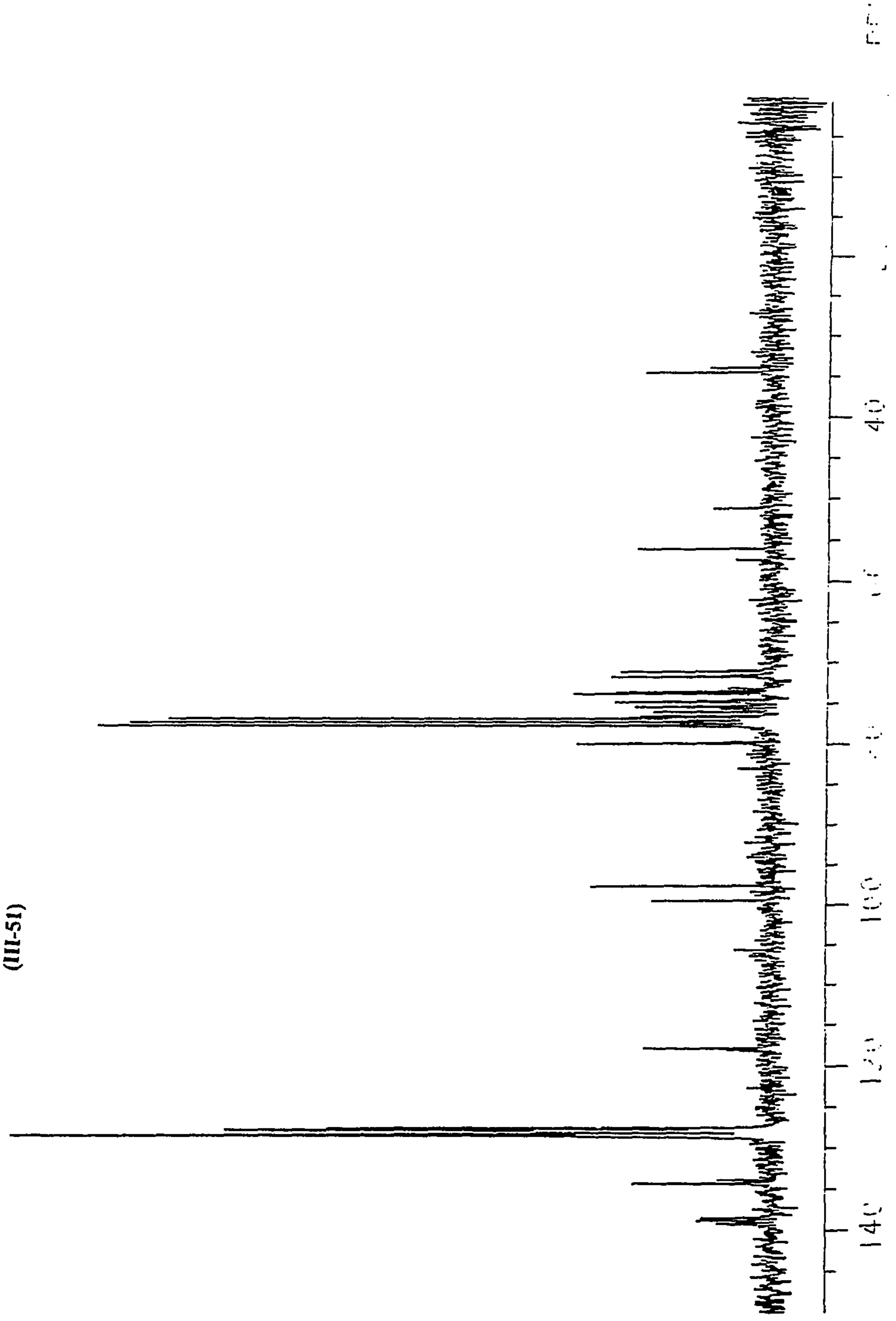


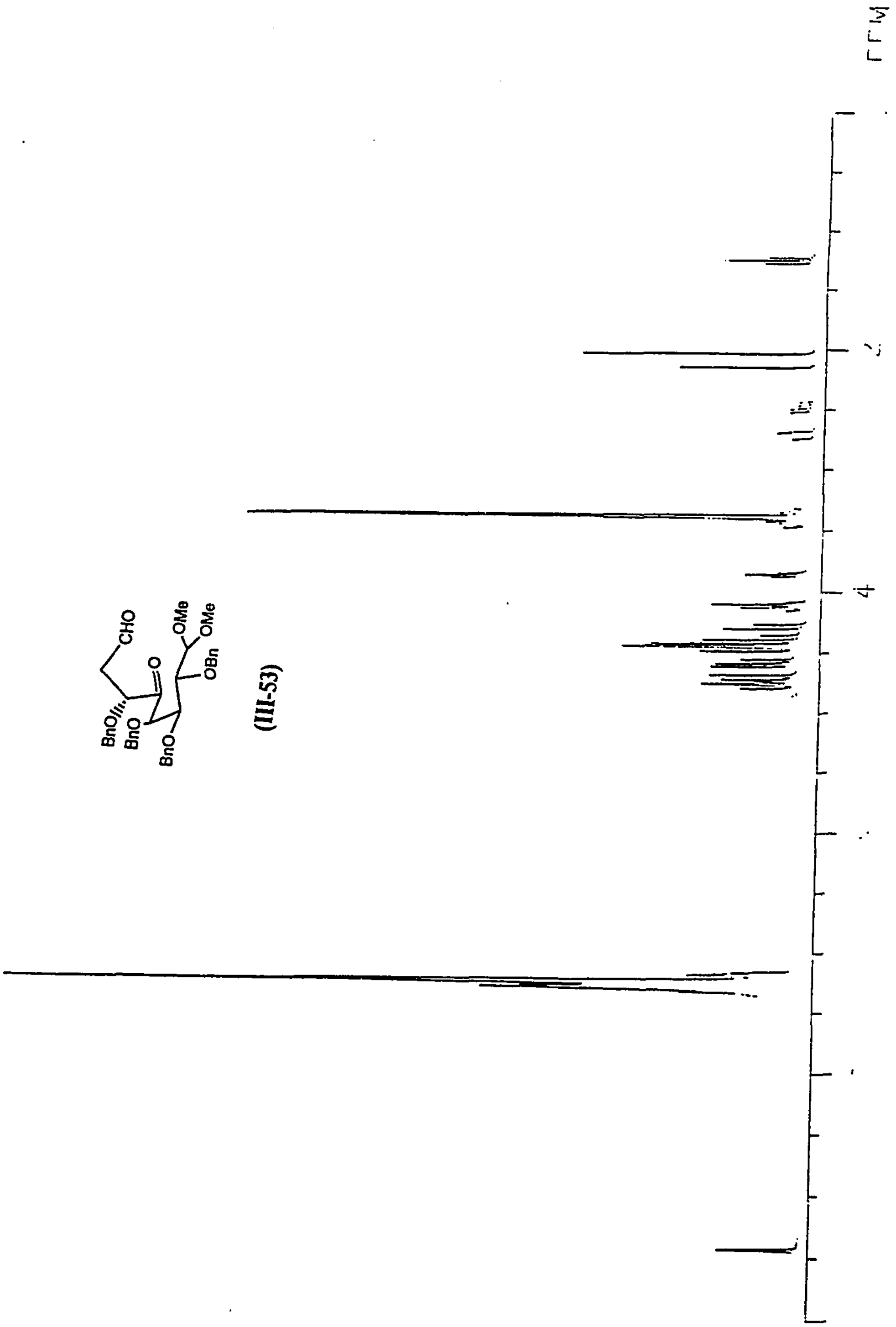
(III-51)



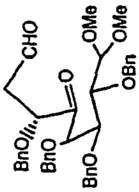


(III-51)

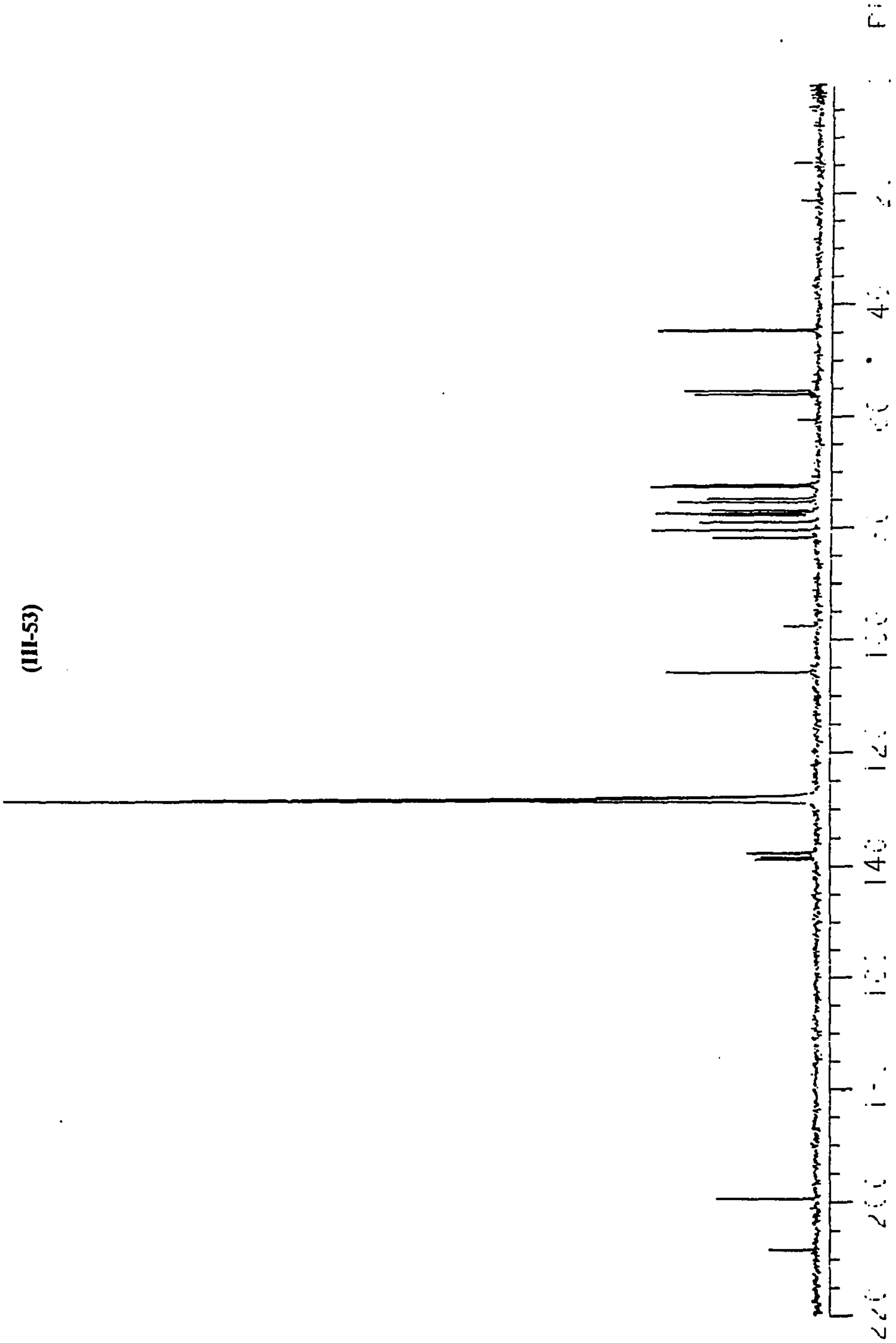


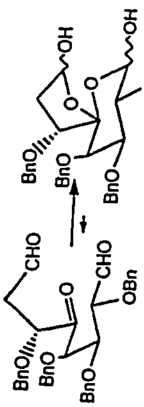


(III-53)



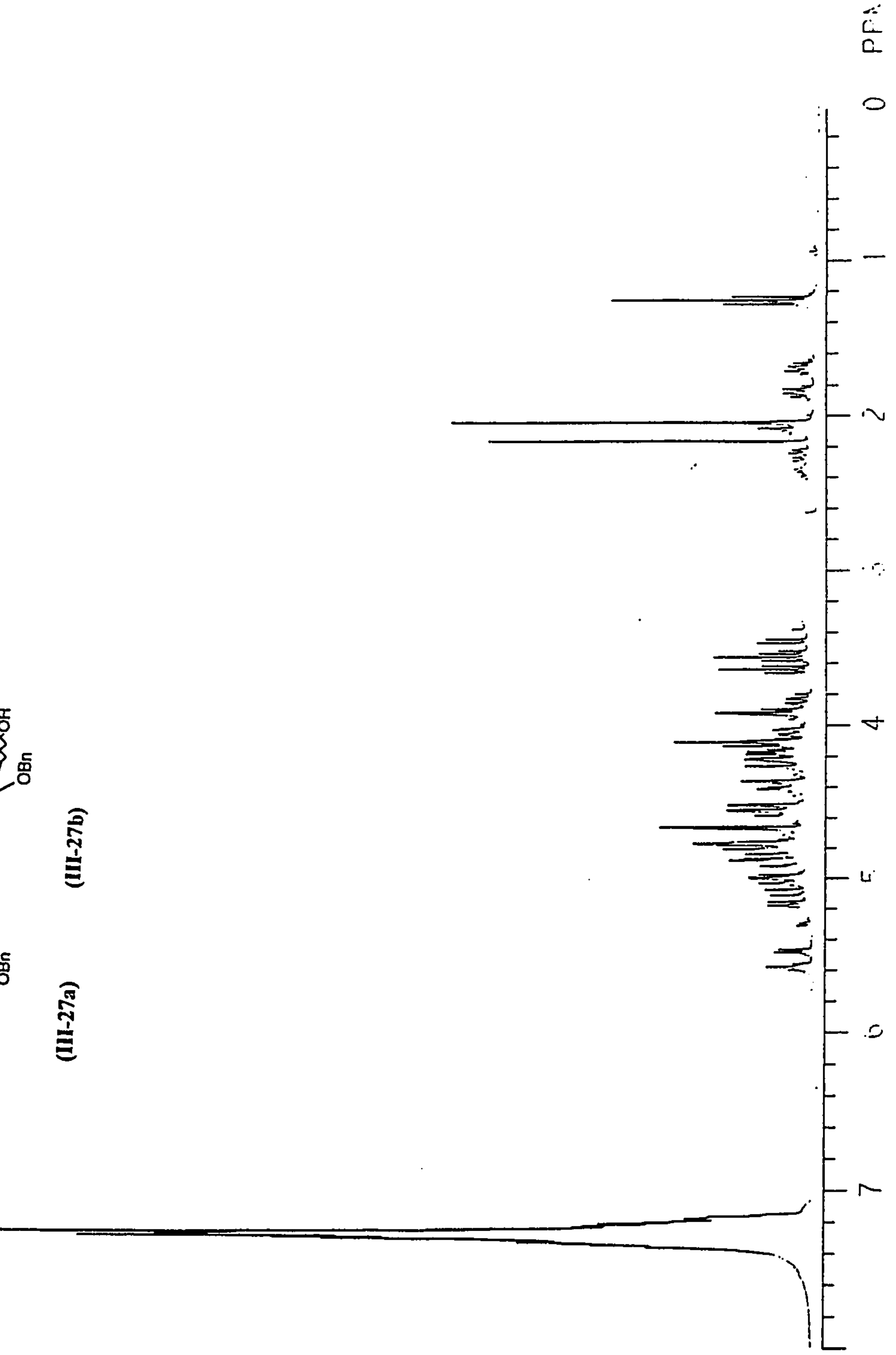
(III-53)

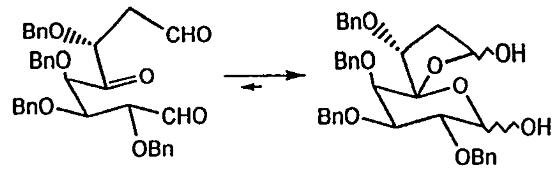




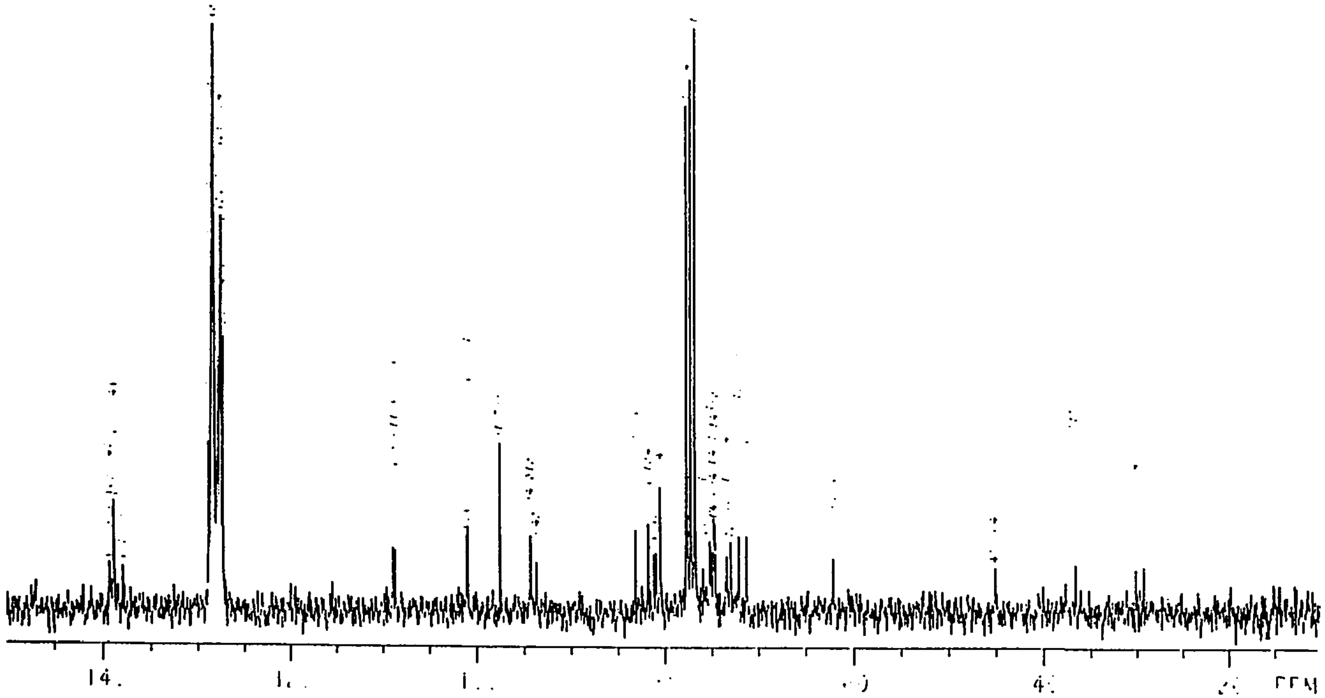
(III-27a)

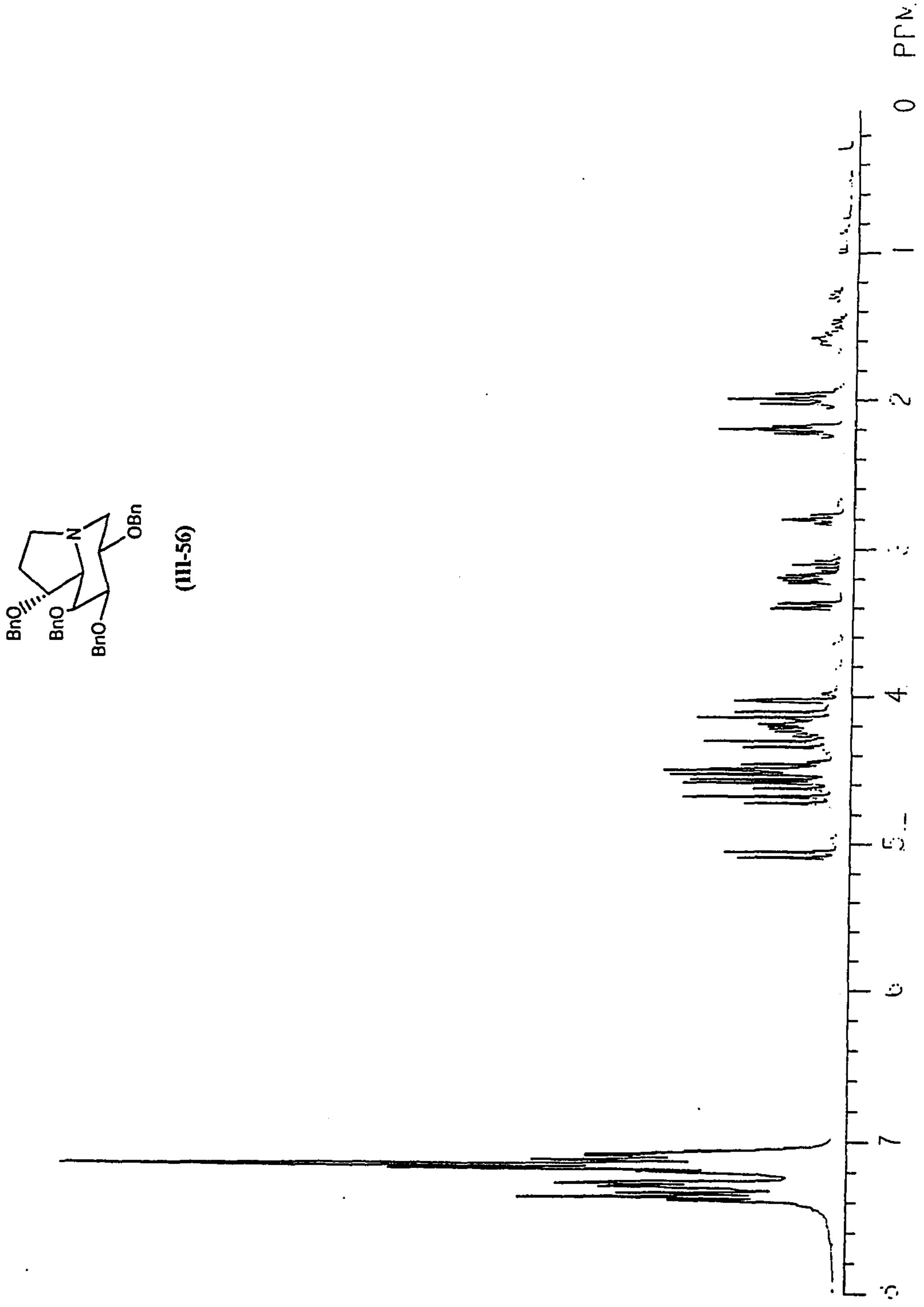
(III-27b)



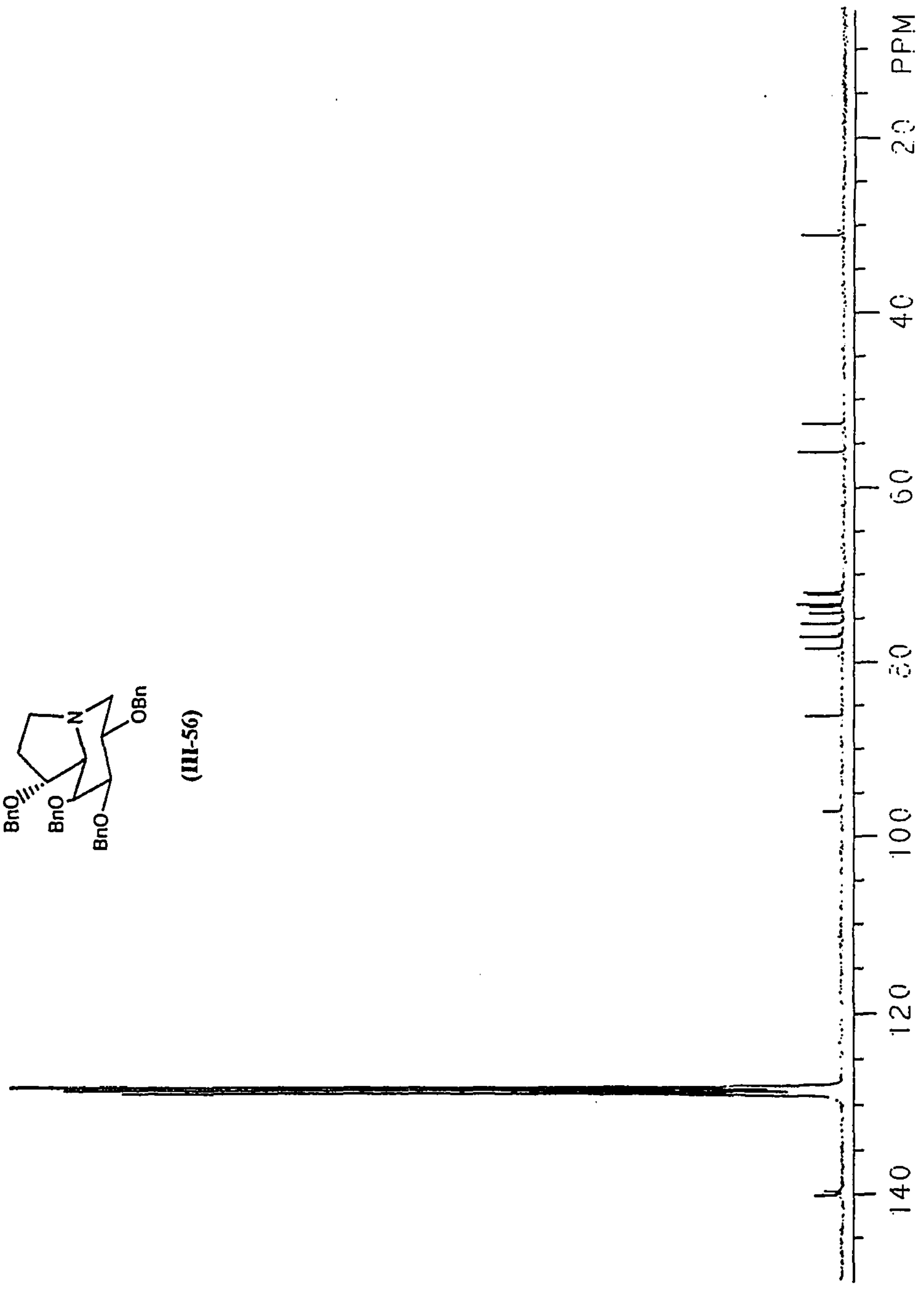


(III-27a) (III-27b)

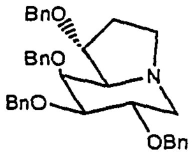




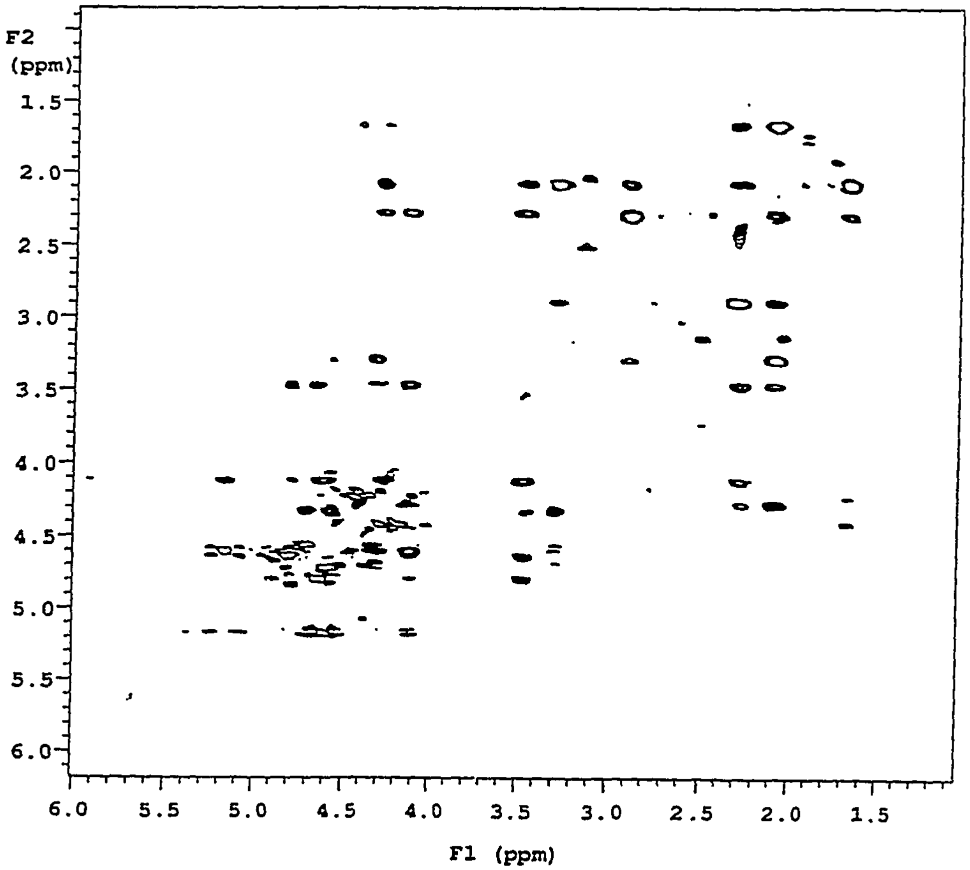
(III-56)

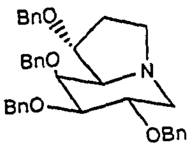


(III-56)

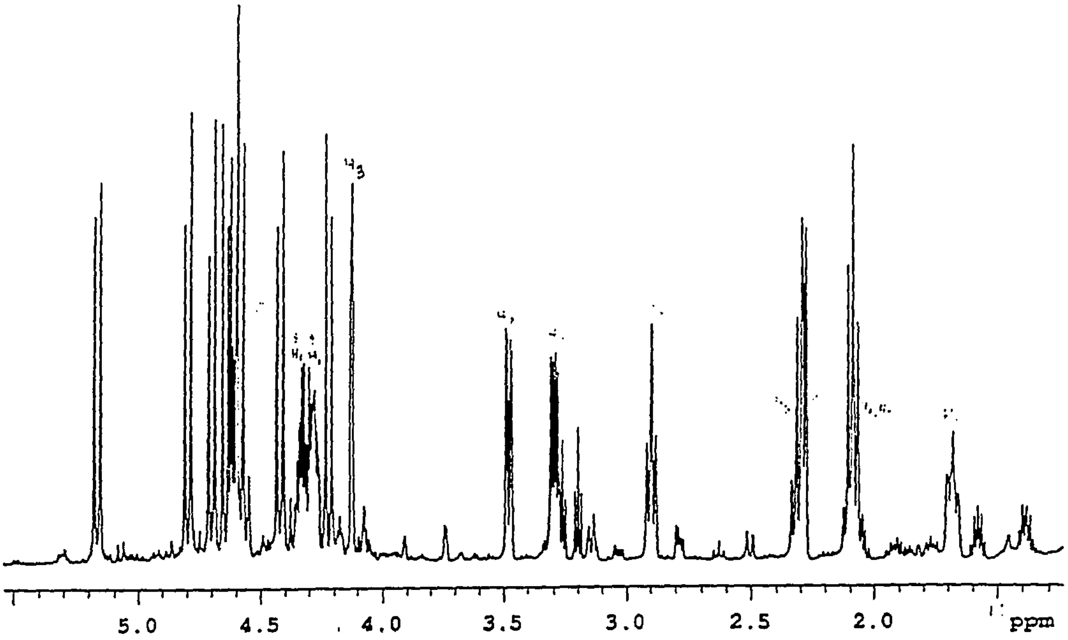

BnO
BnO
BnO
N
OBn

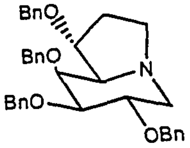
(III-56)


F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F1 (ppm)

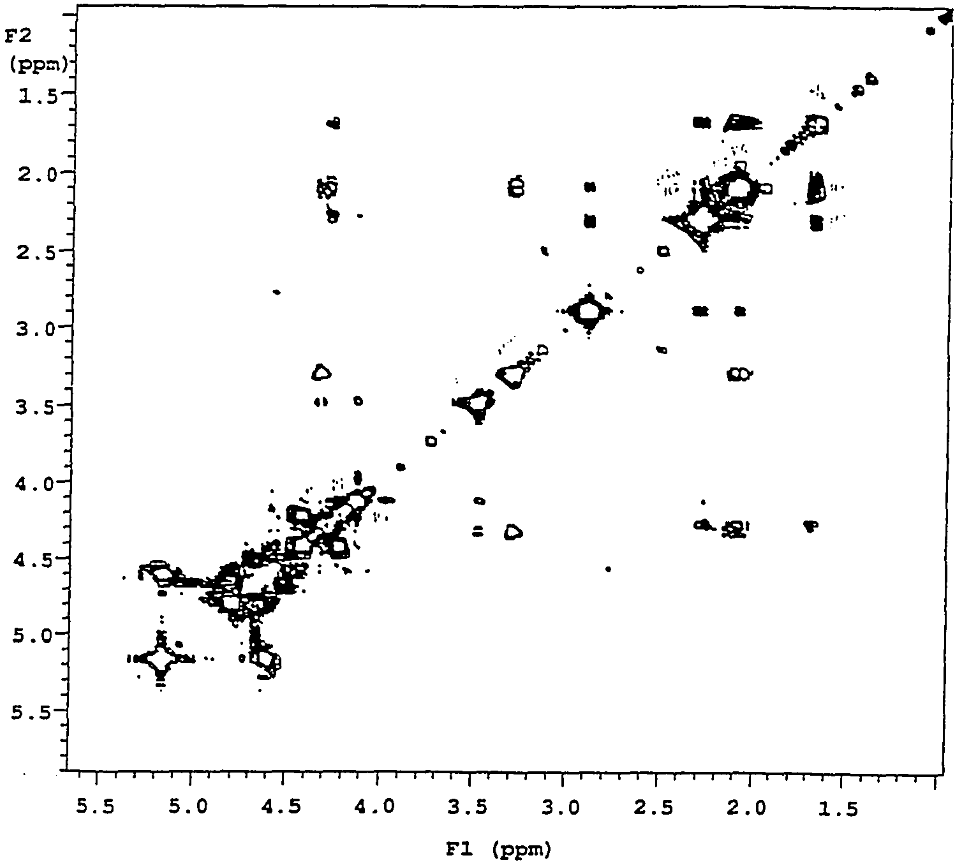


(III-56)

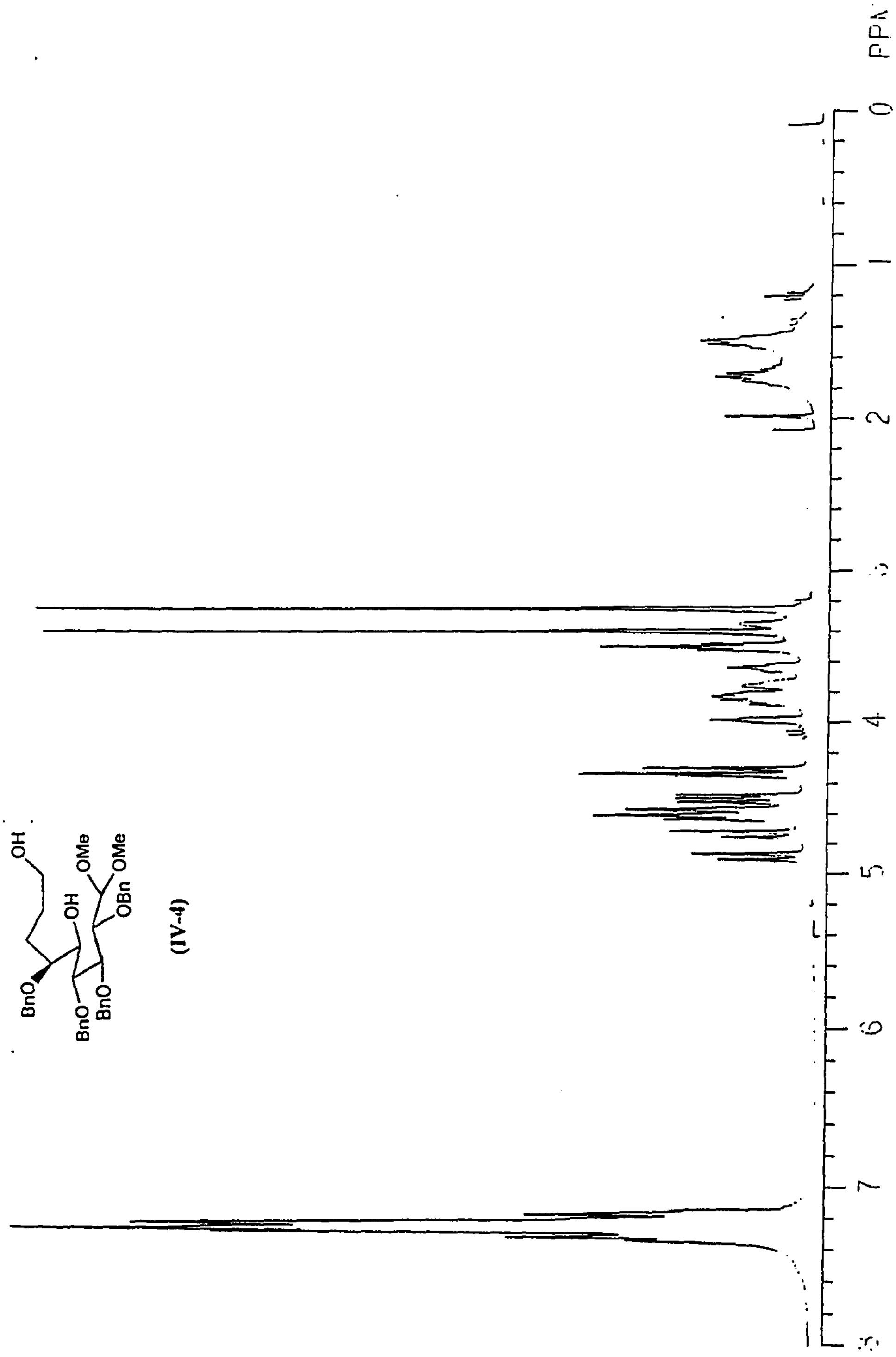


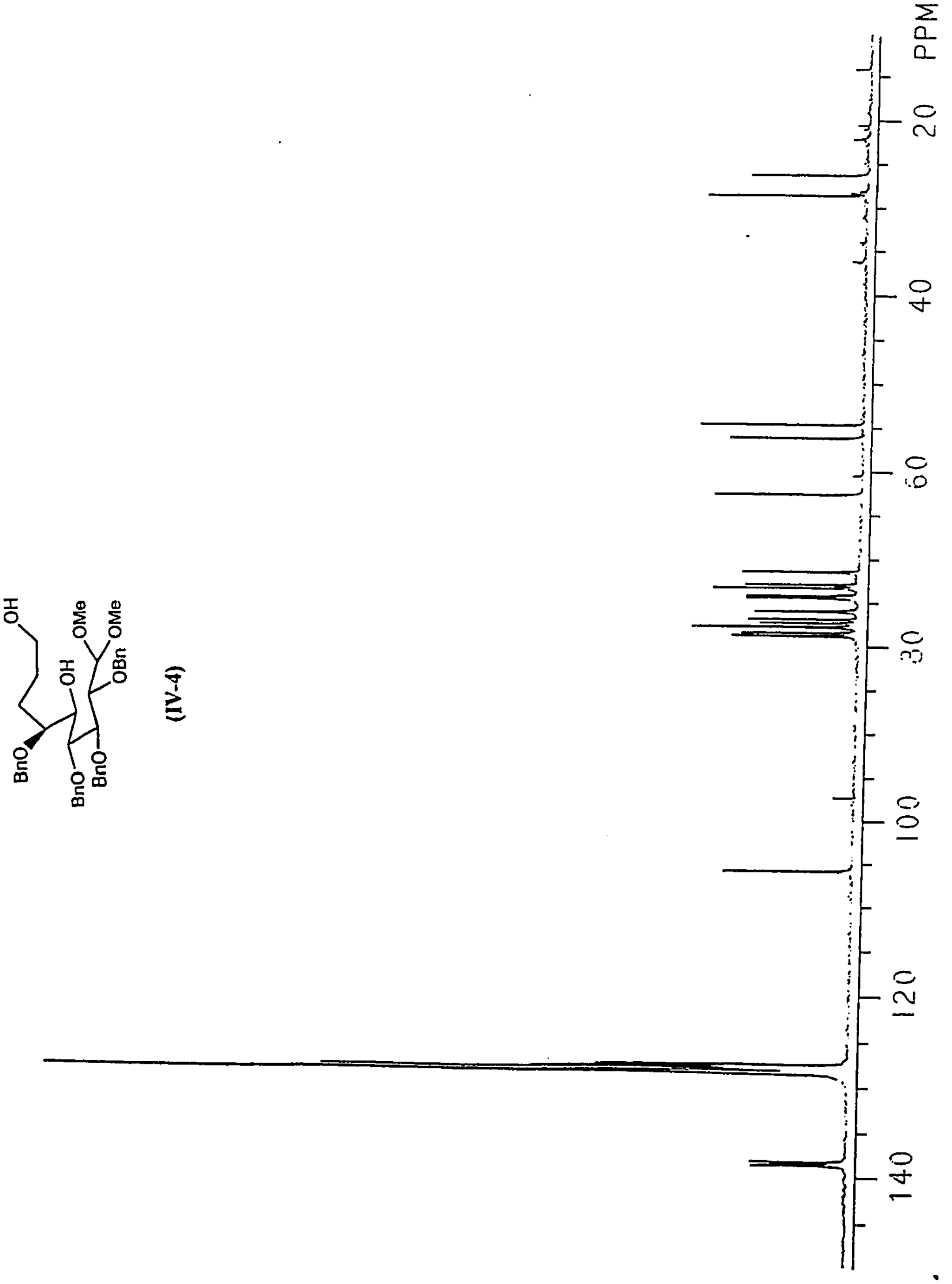

BnO
BnO
BnO
N
OBn

(III-56)

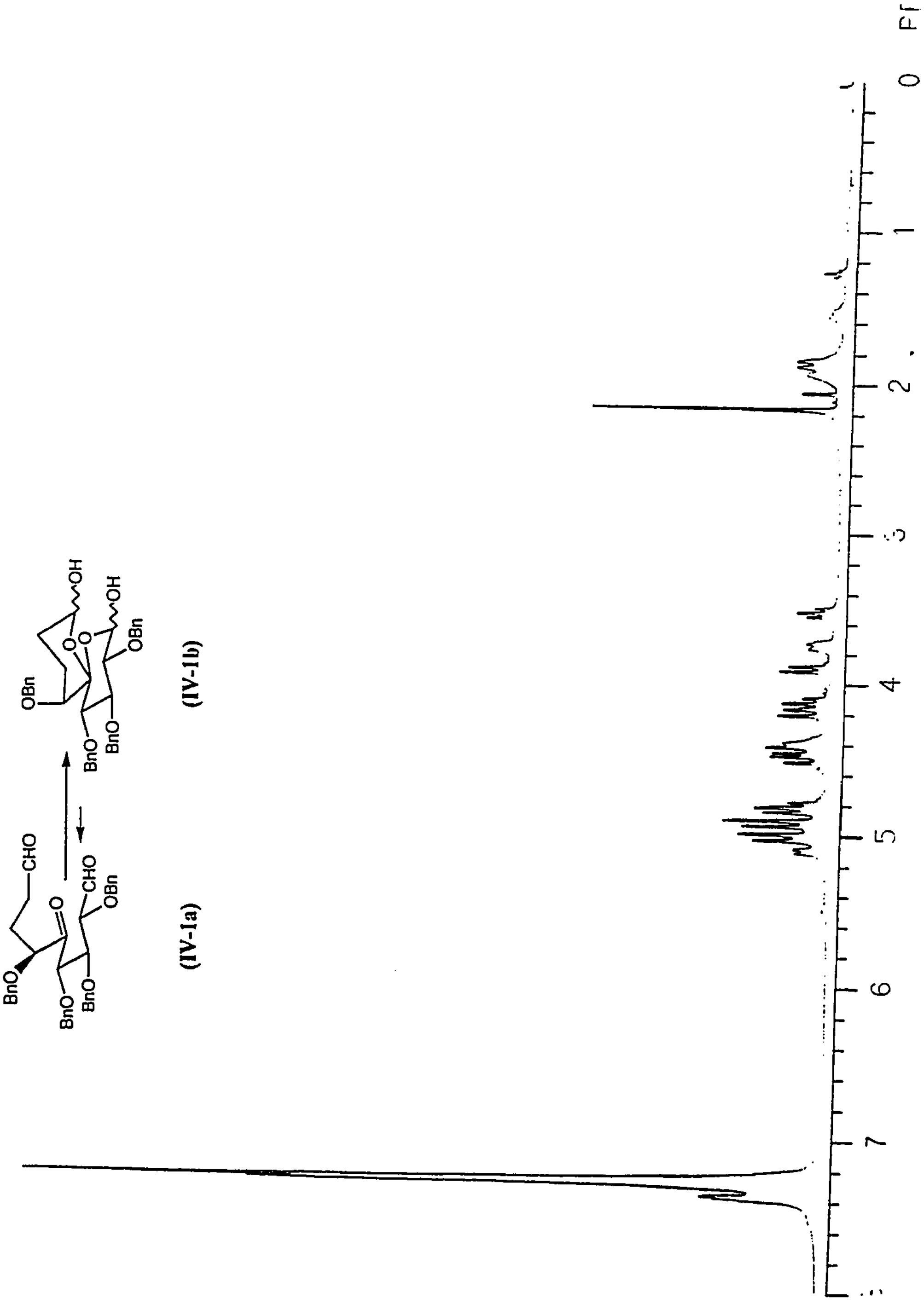

F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
F1 (ppm)

(IV-4)



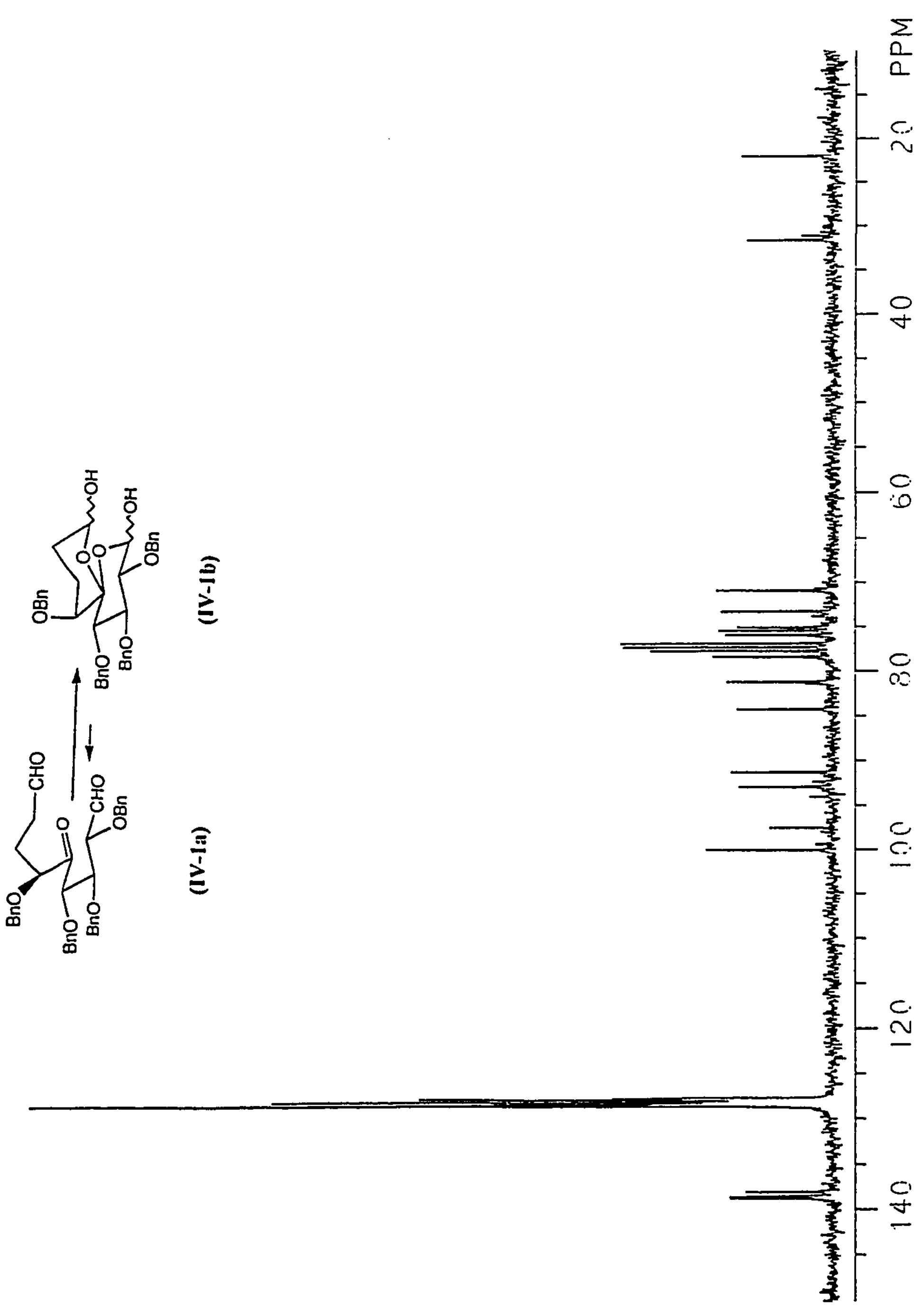


(IV-4)



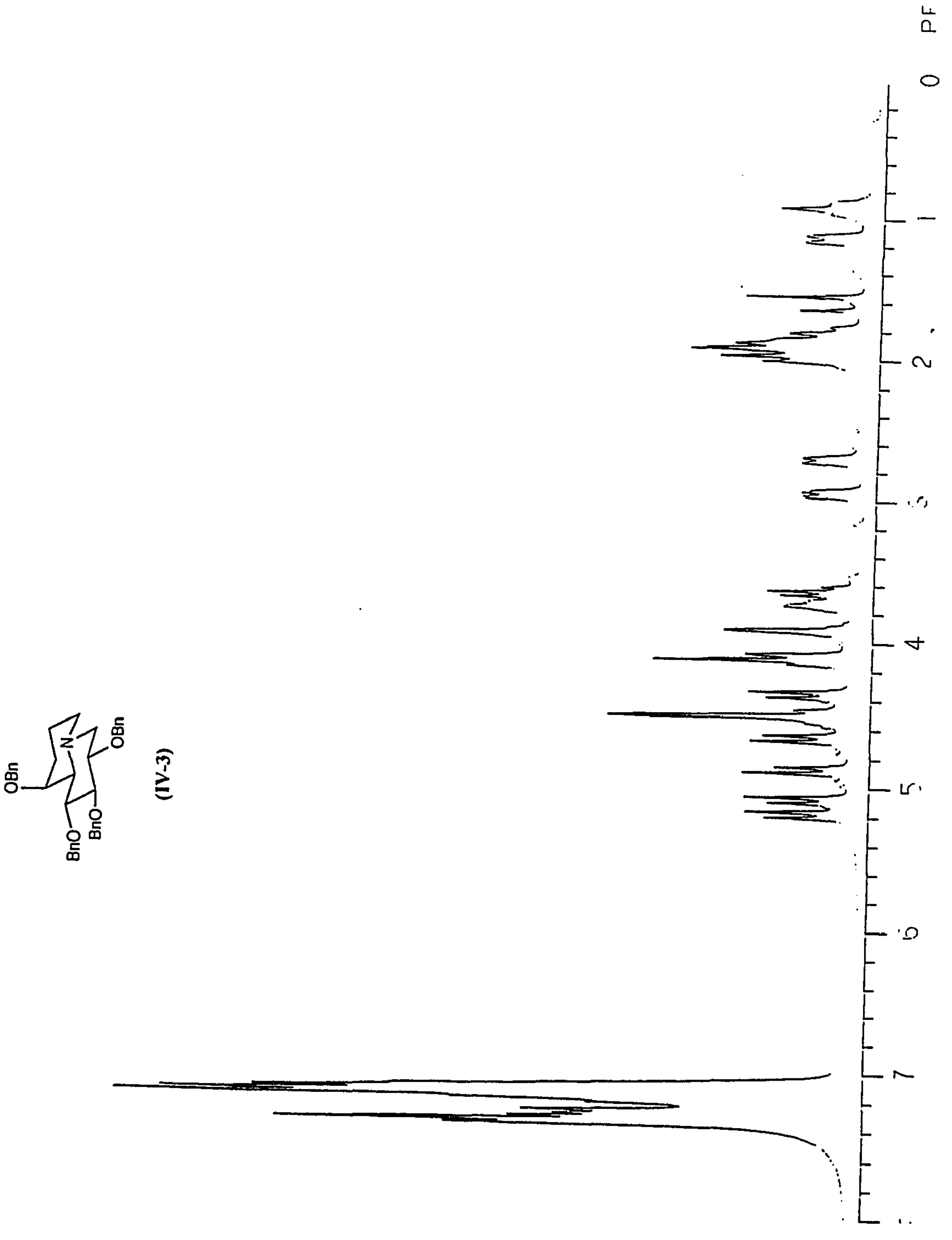
(IV-1a)

(IV-1b)

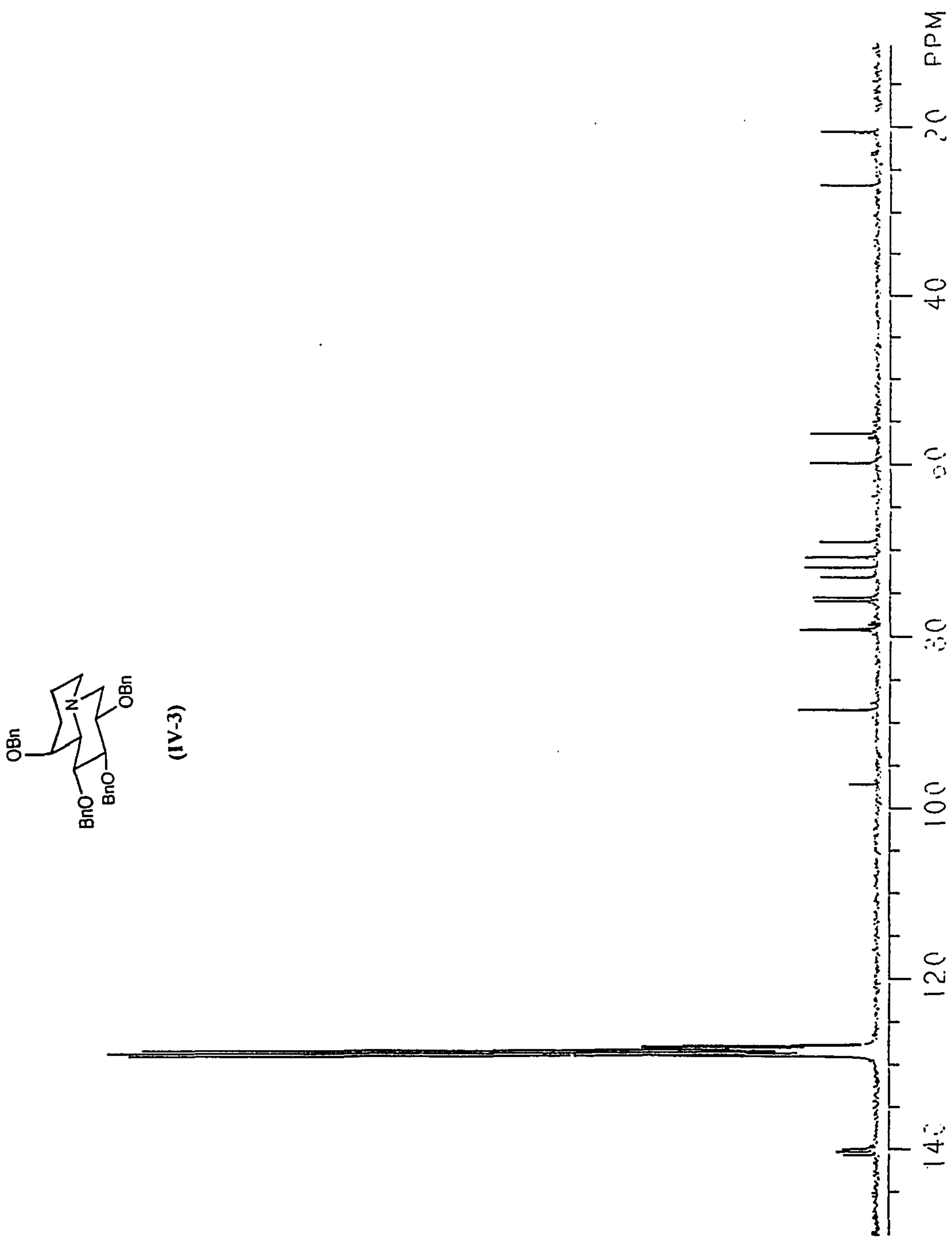

BnO
BnO
BnO
O
CHO
CHO
OBn
OBn
BnO
BnO
O
O
OH
OH
OBn
PPM
20
40
60
80
100
120
140

(IV-1a)

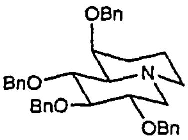
(IV-1b)



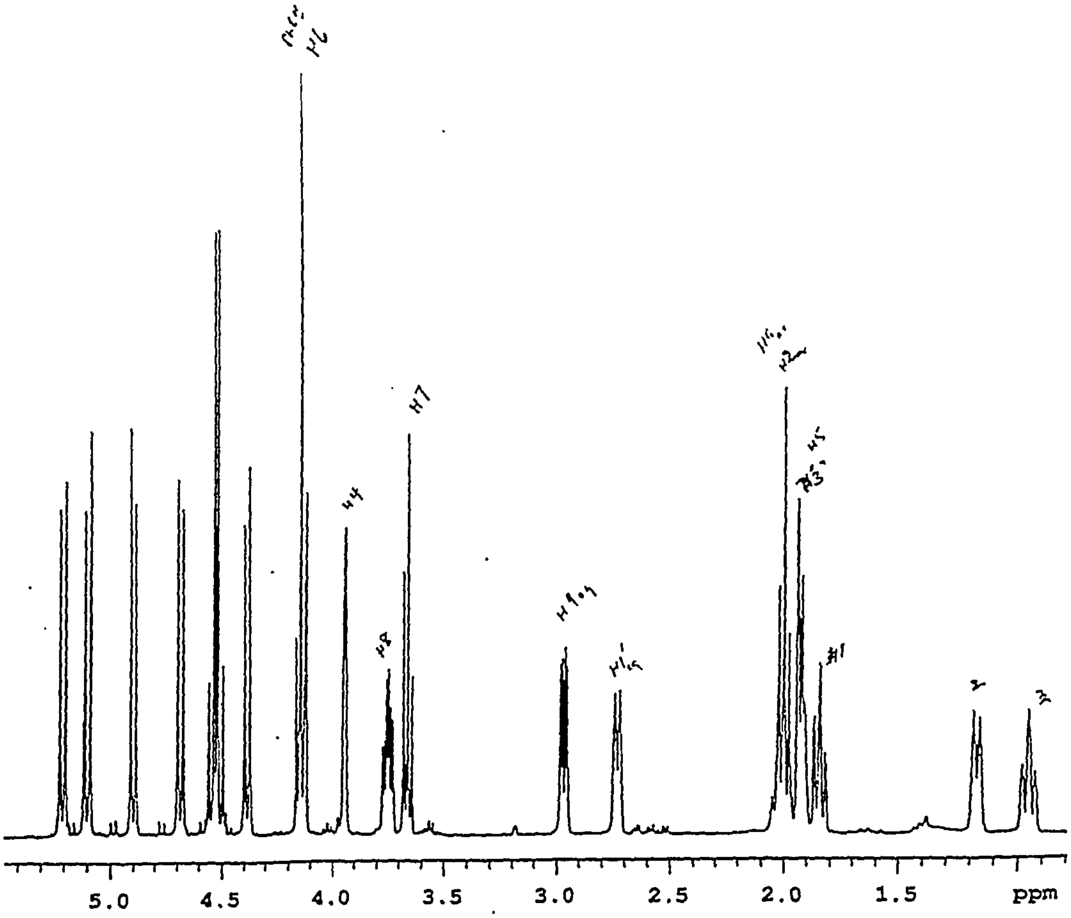
(IV-3)

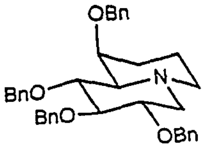


(IV-3)

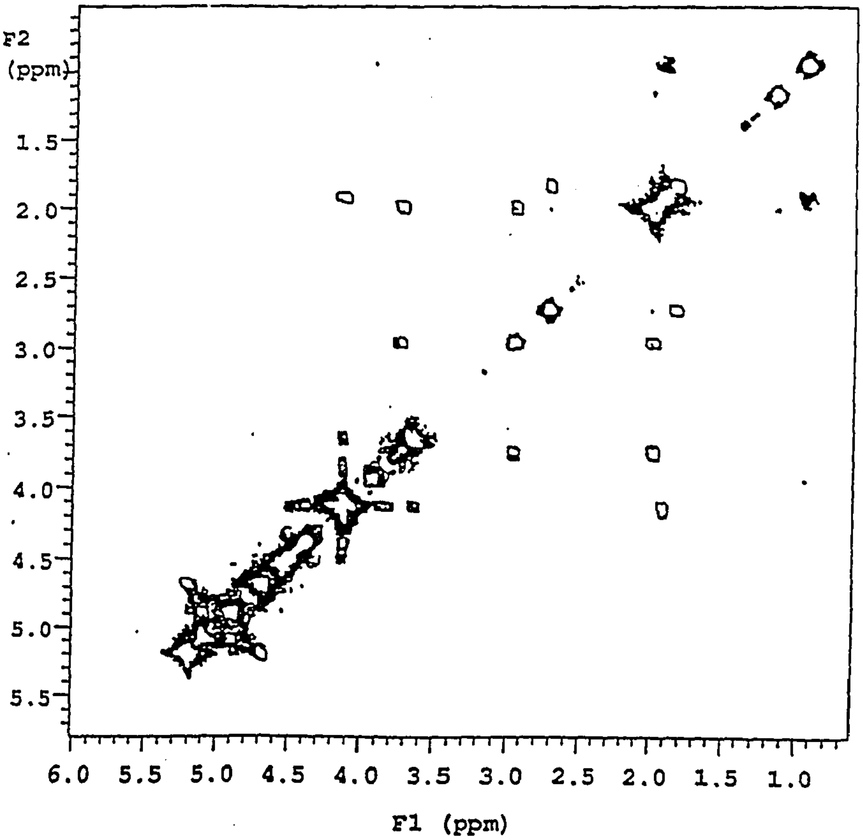


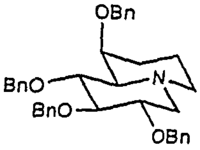
(IV-3)



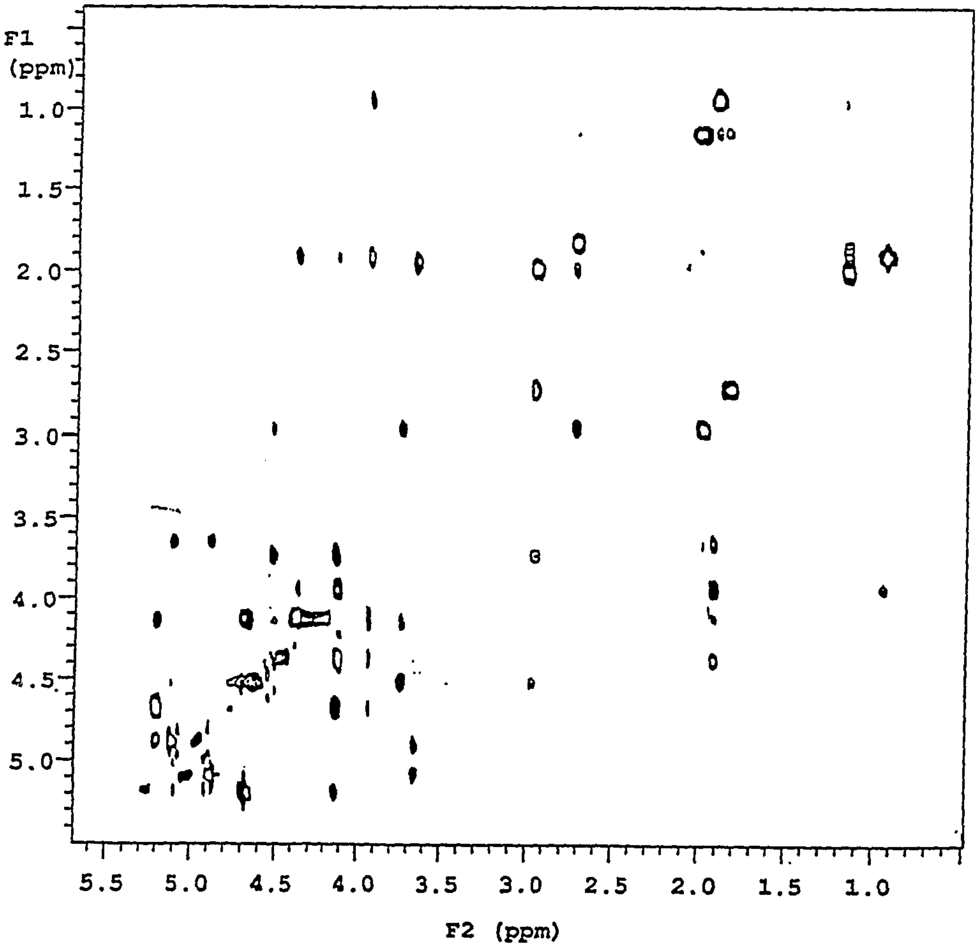

OBn
BnO
BnO
N
OBn

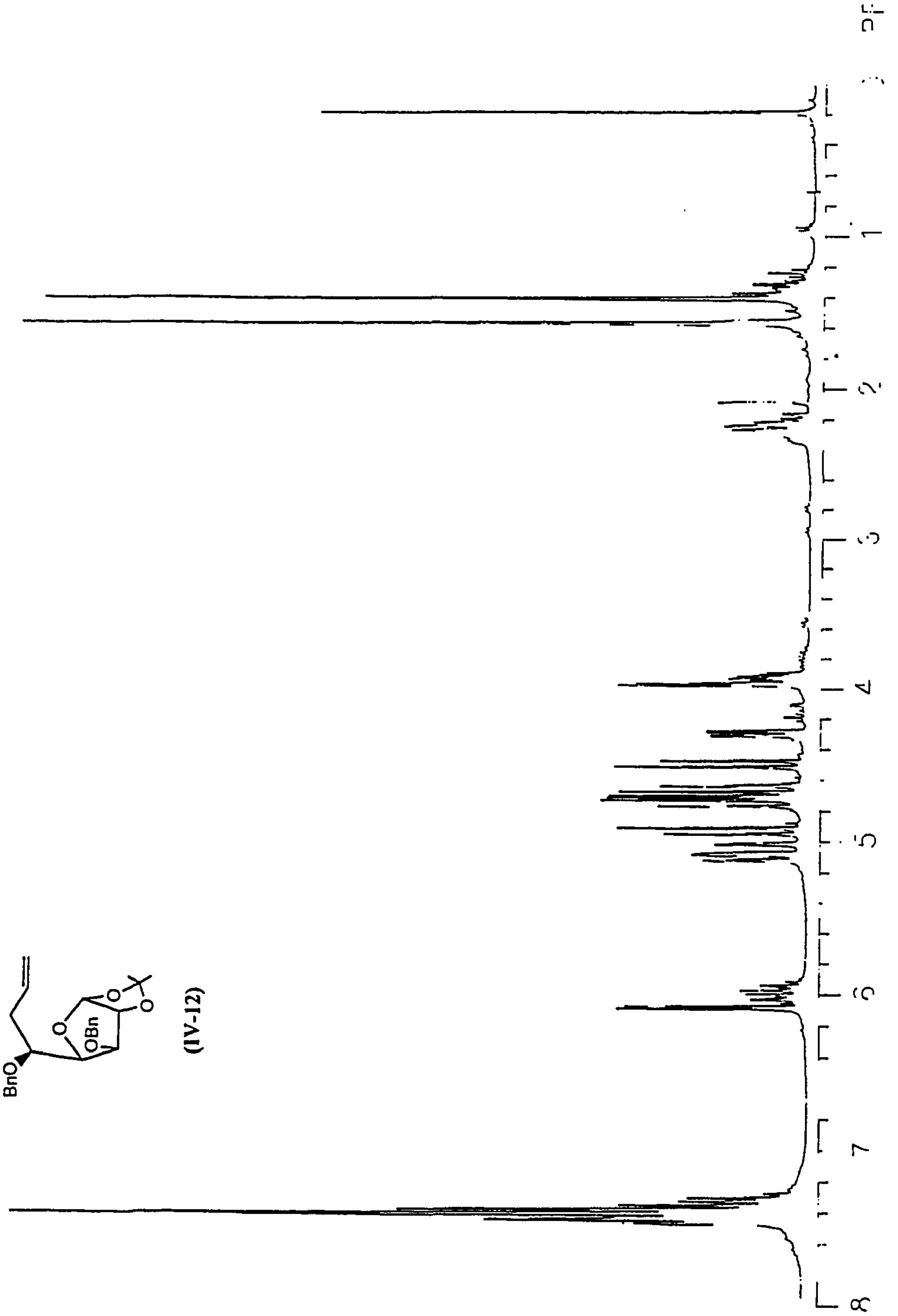
(IV-3)


F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

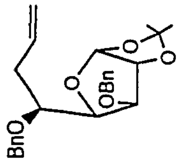

OBn
BnO
BnO
N
OBn

(IV-3)

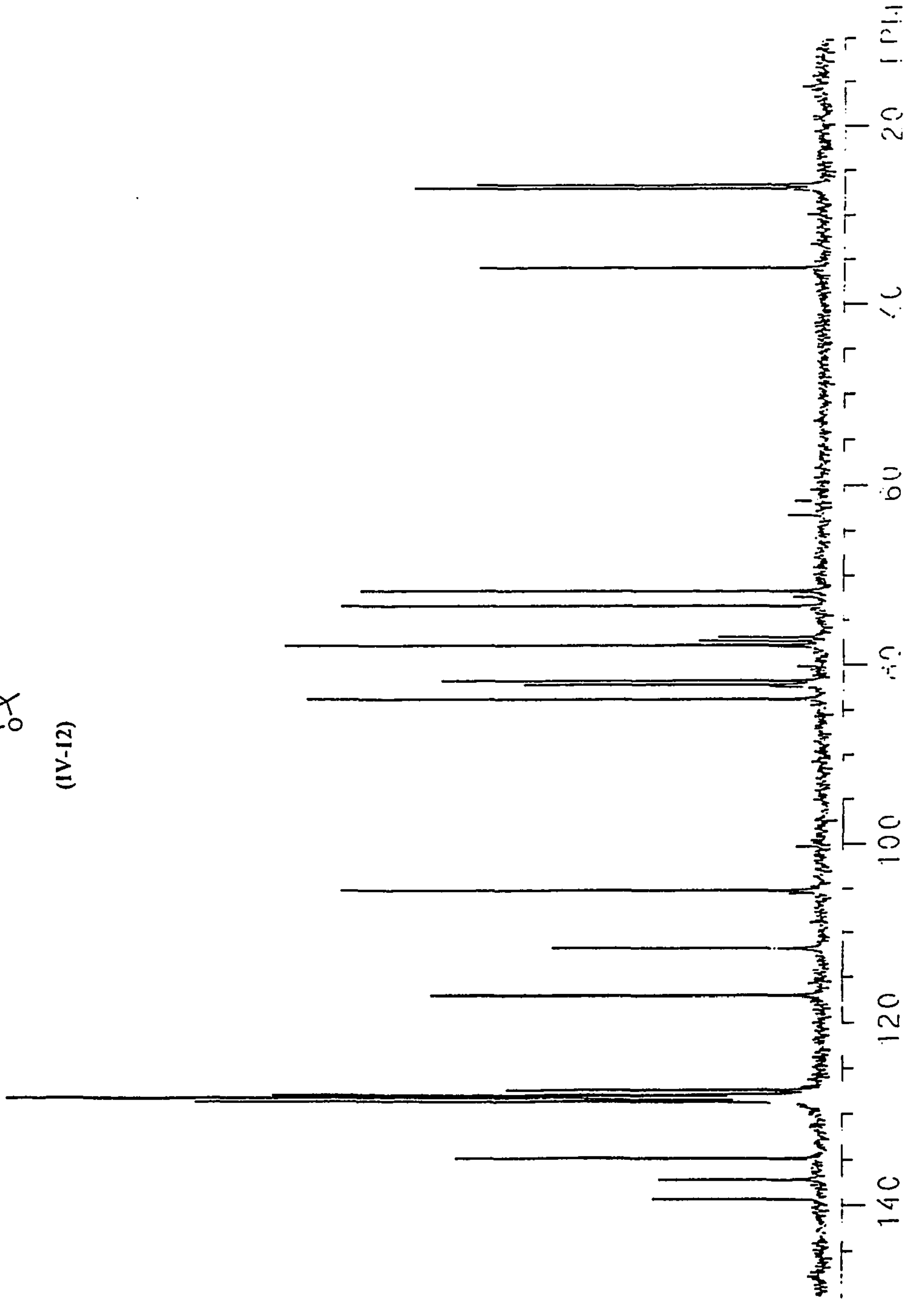

F1 (ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F2 (ppm)

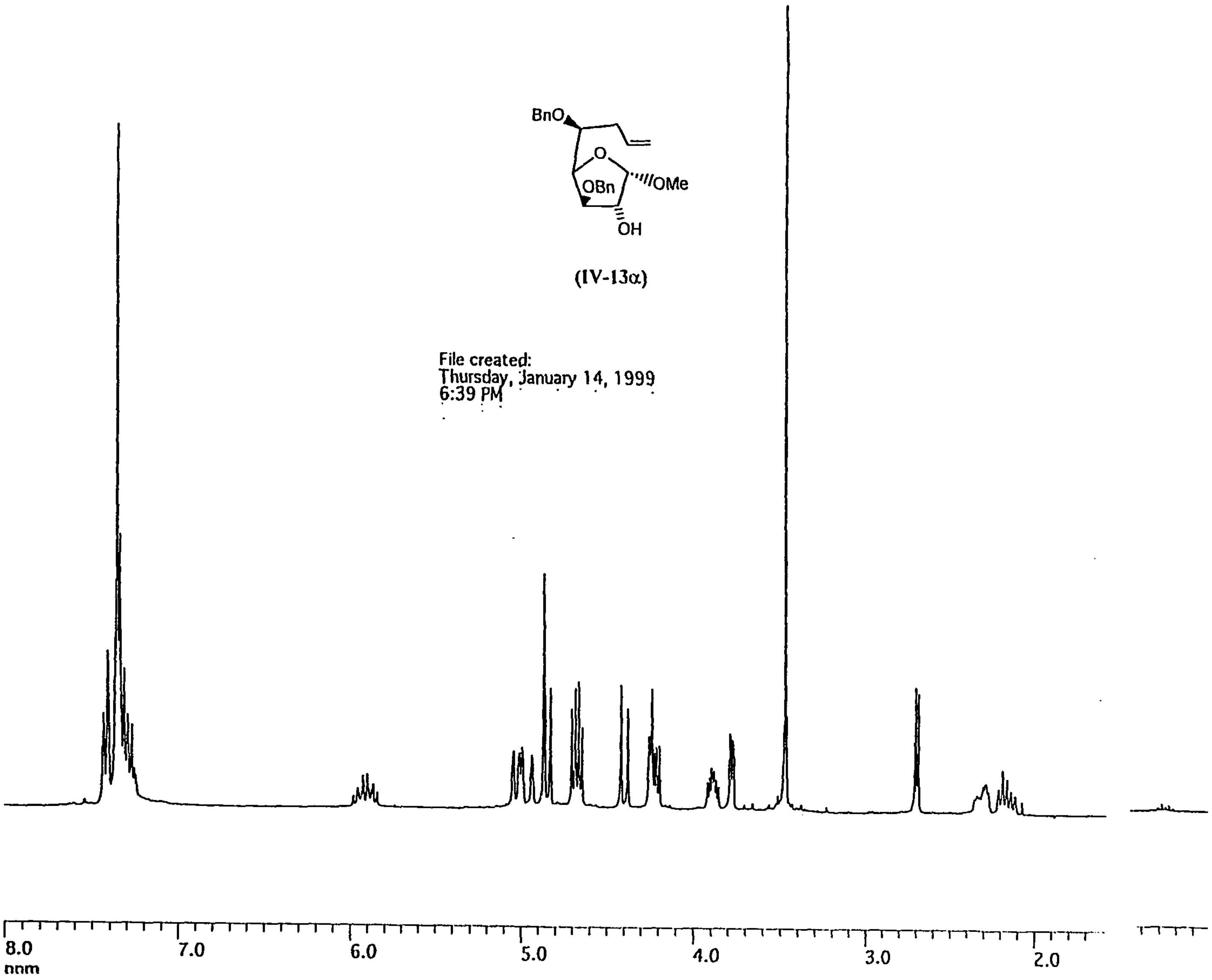


(IV-12)



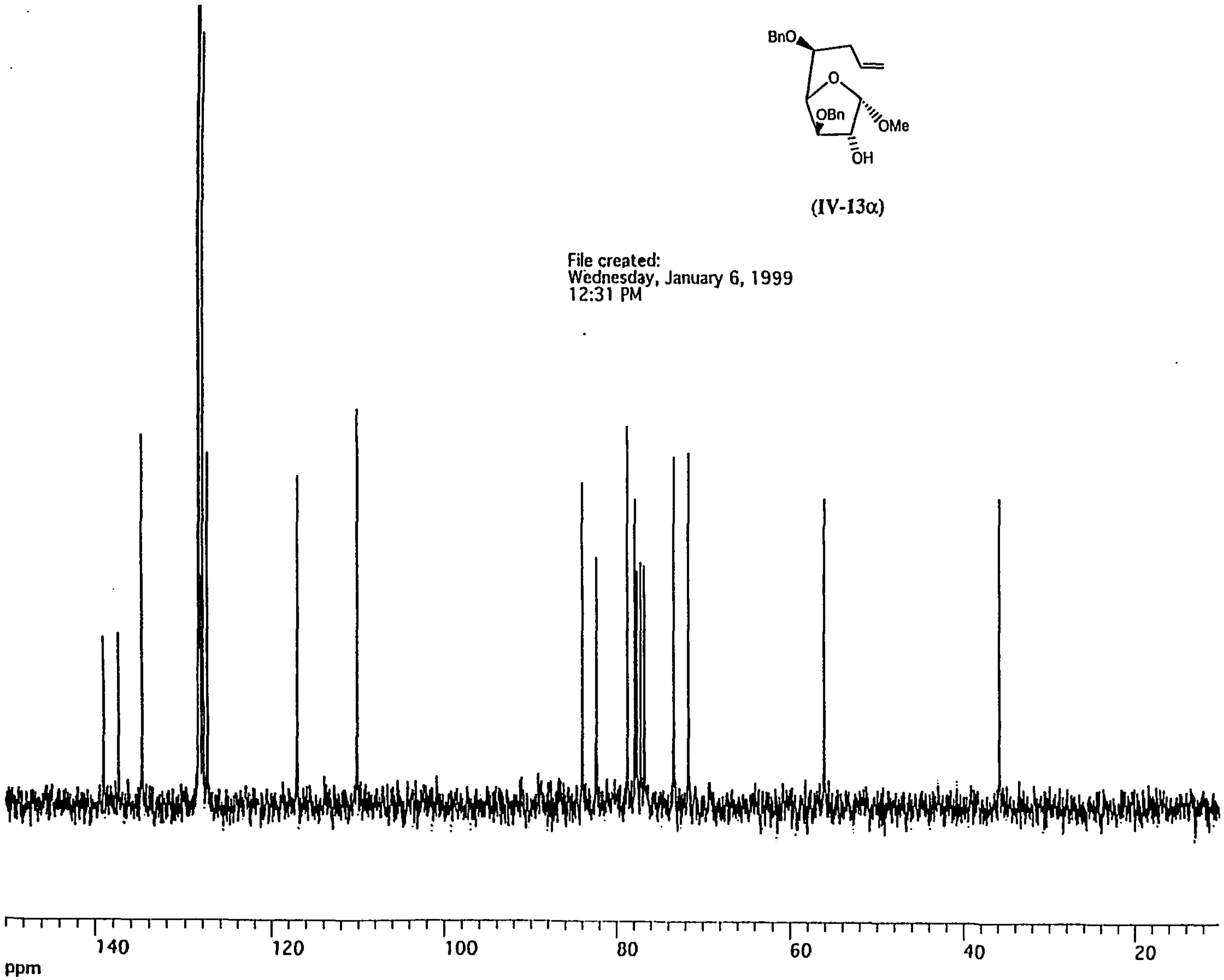
(IV-12)





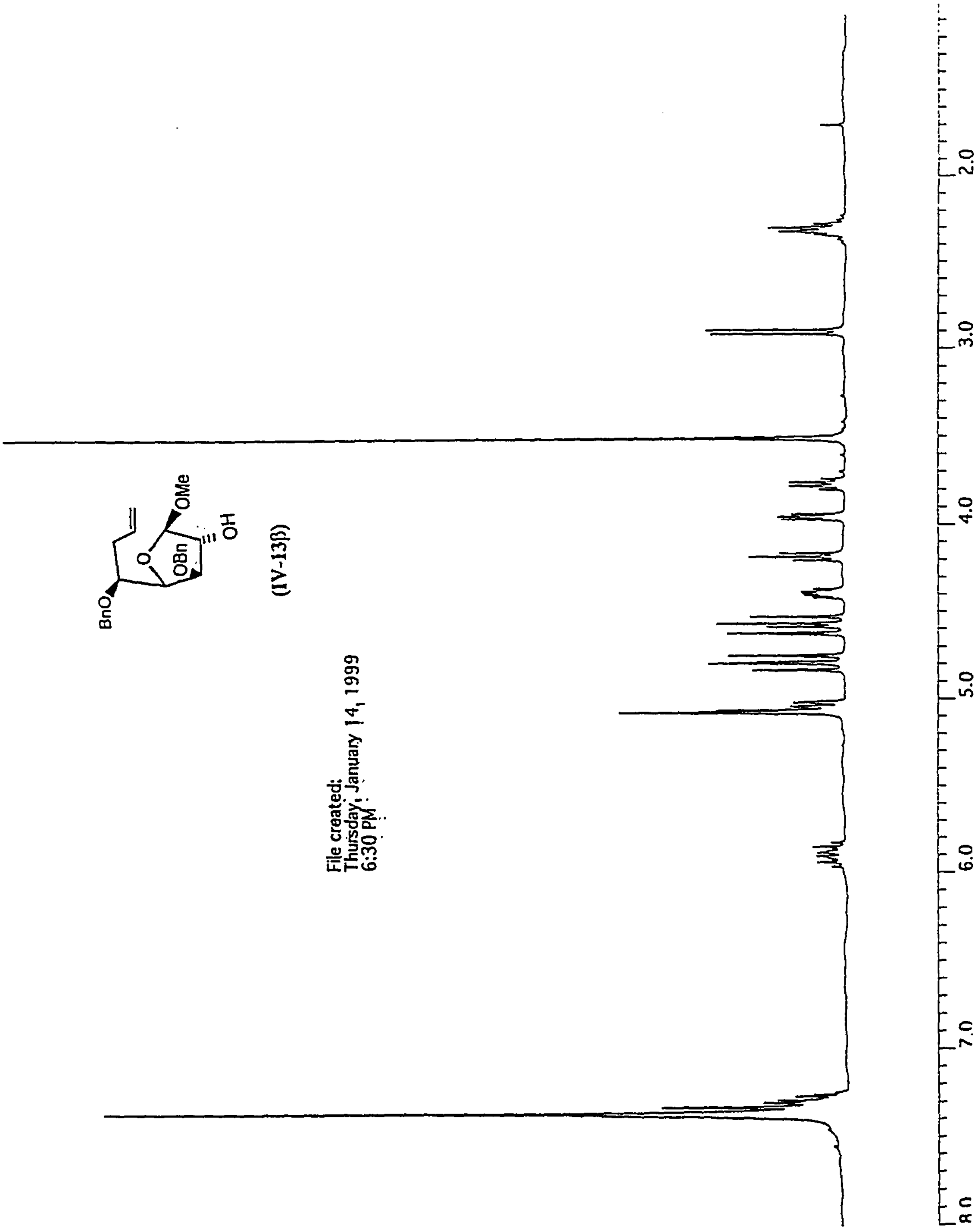
(IV-13α)

File created:
Thursday, January 14, 1999
6:39 PM



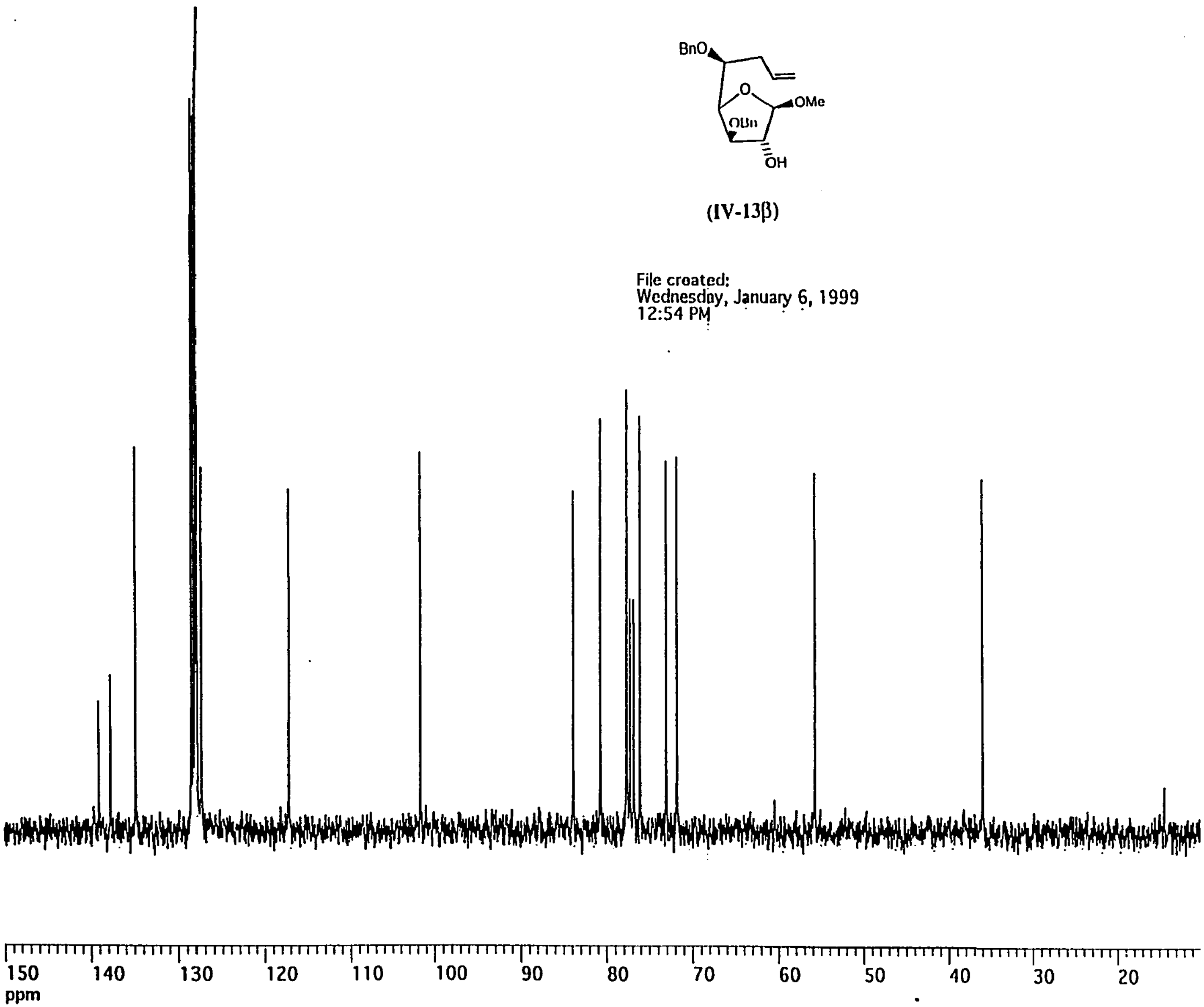
(IV-13α)

File created:
Wednesday, January 6, 1999
12:31 PM



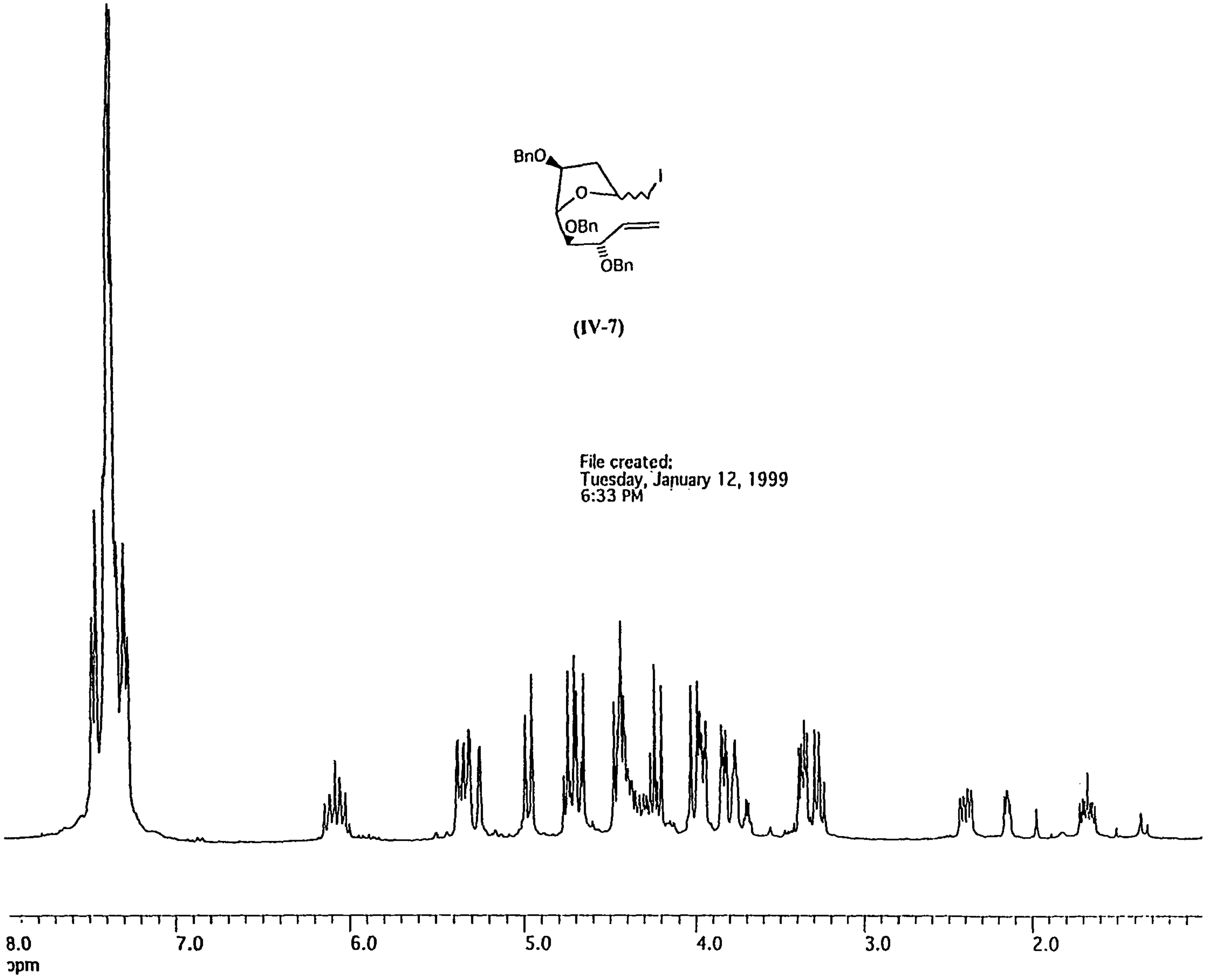
(IV-13β)

File created:
Thursday, January 14, 1999
6:30 PM



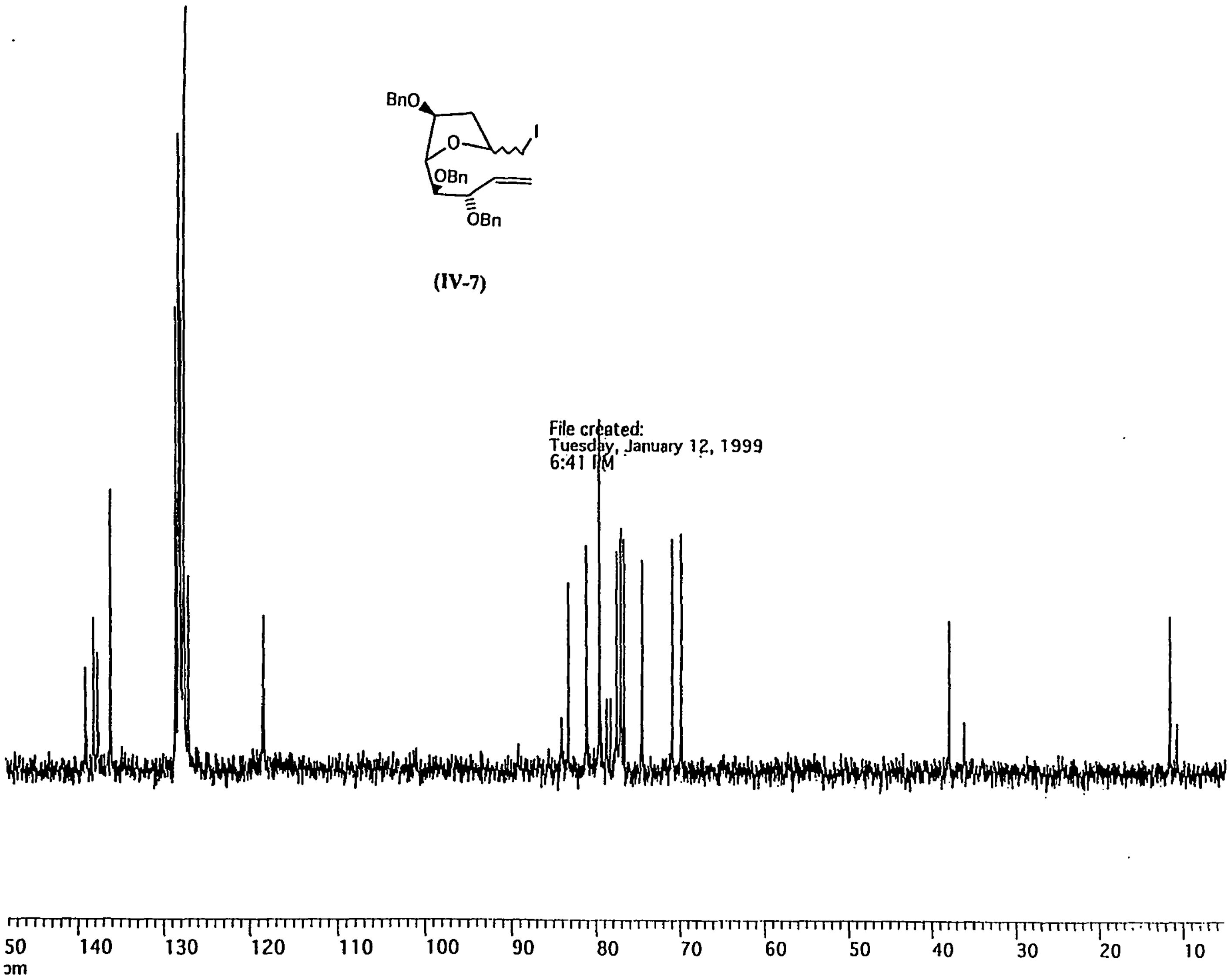
(IV-13β)

File created:
Wednesday, January 6, 1999
12:54 PM



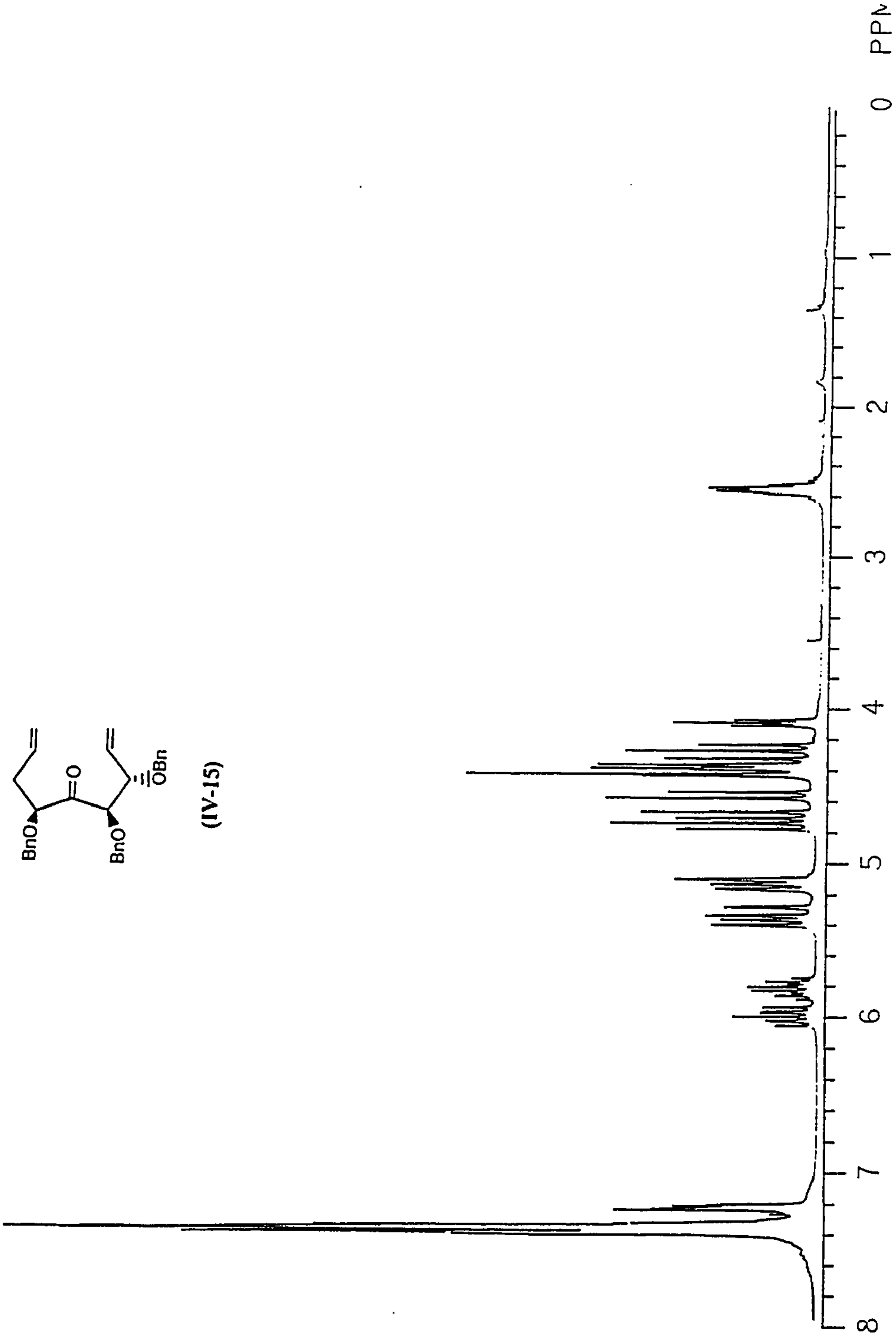
(IV-7)

File created:
Tuesday, January 12, 1999
6:33 PM

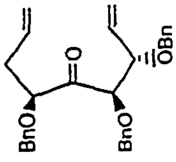


(IV-7)

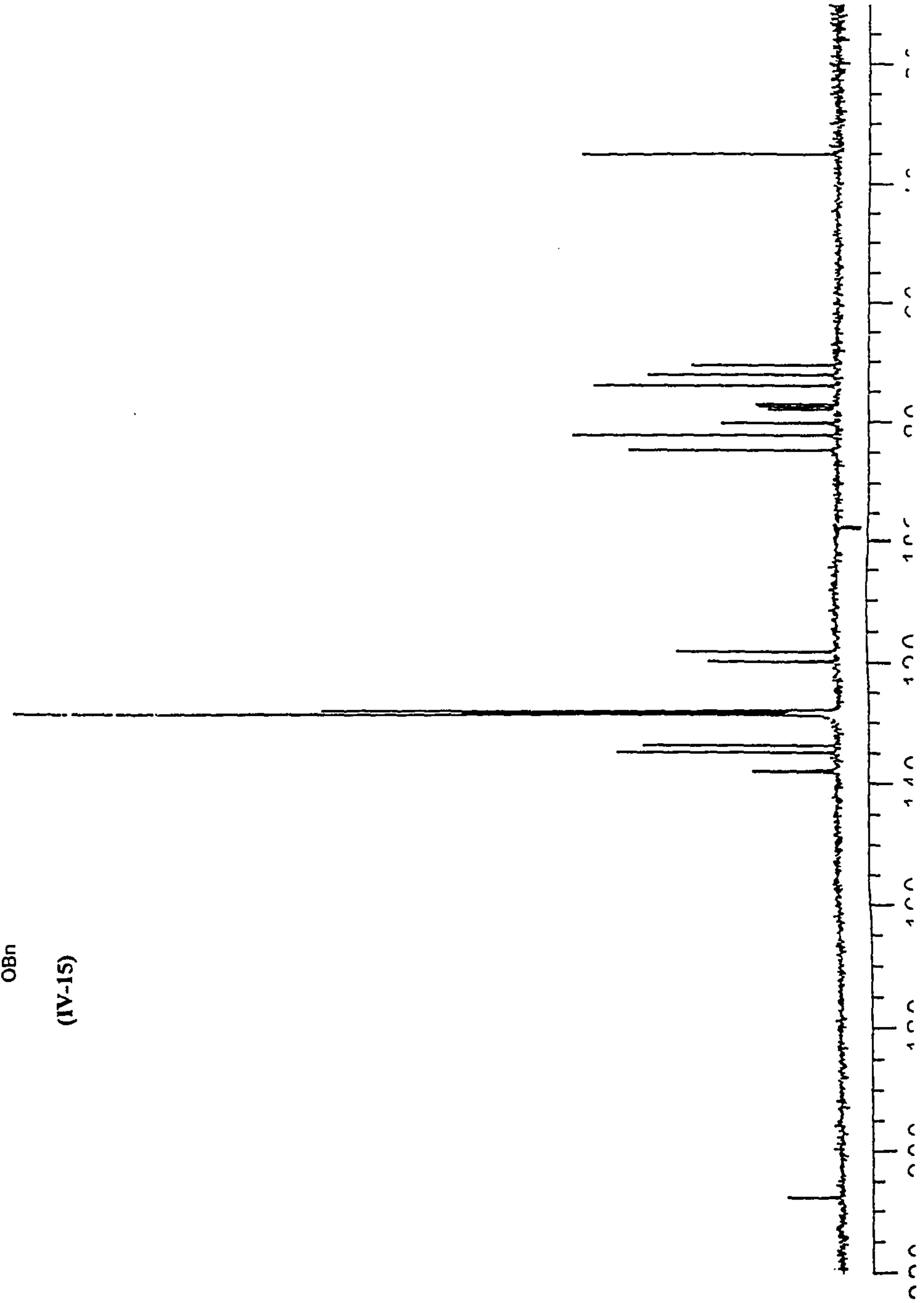
File created:
Tuesday, January 12, 1999
6:41 PM

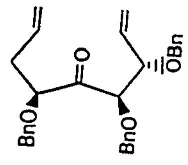


(IV-15)

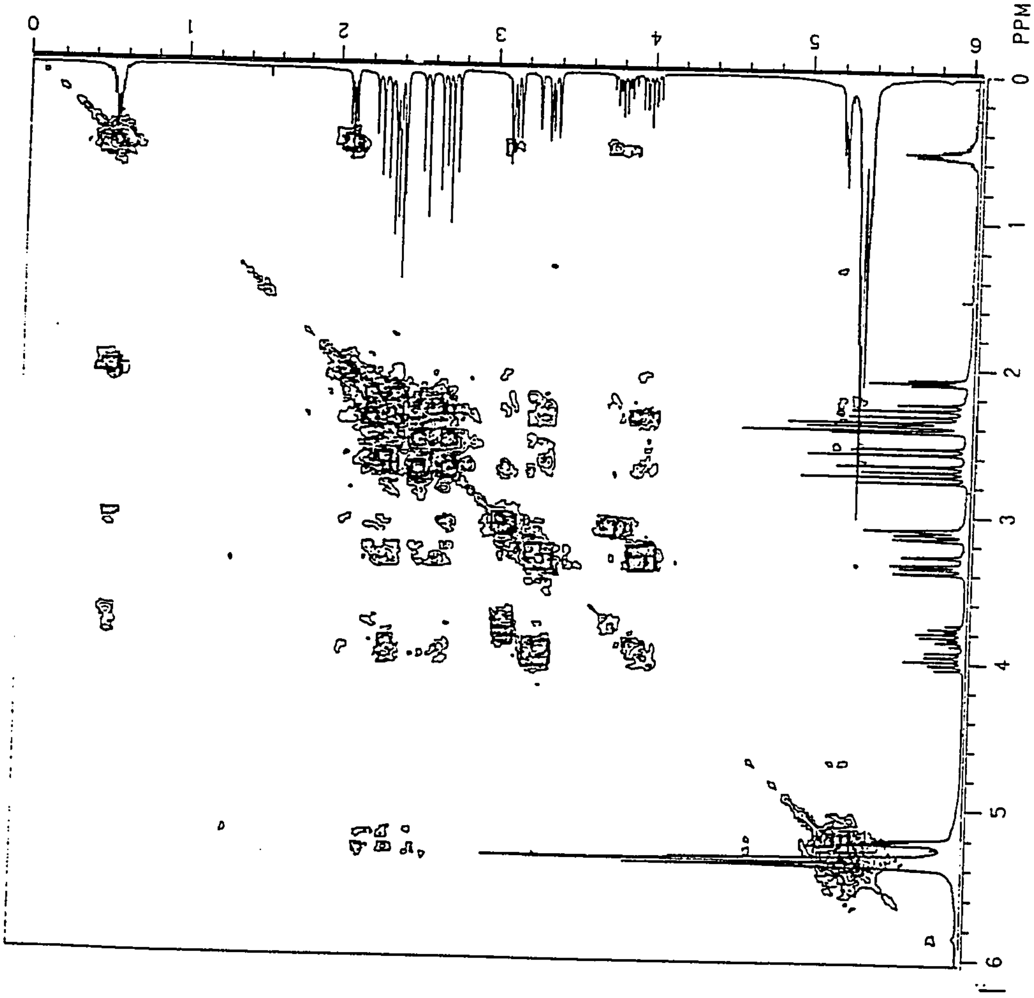


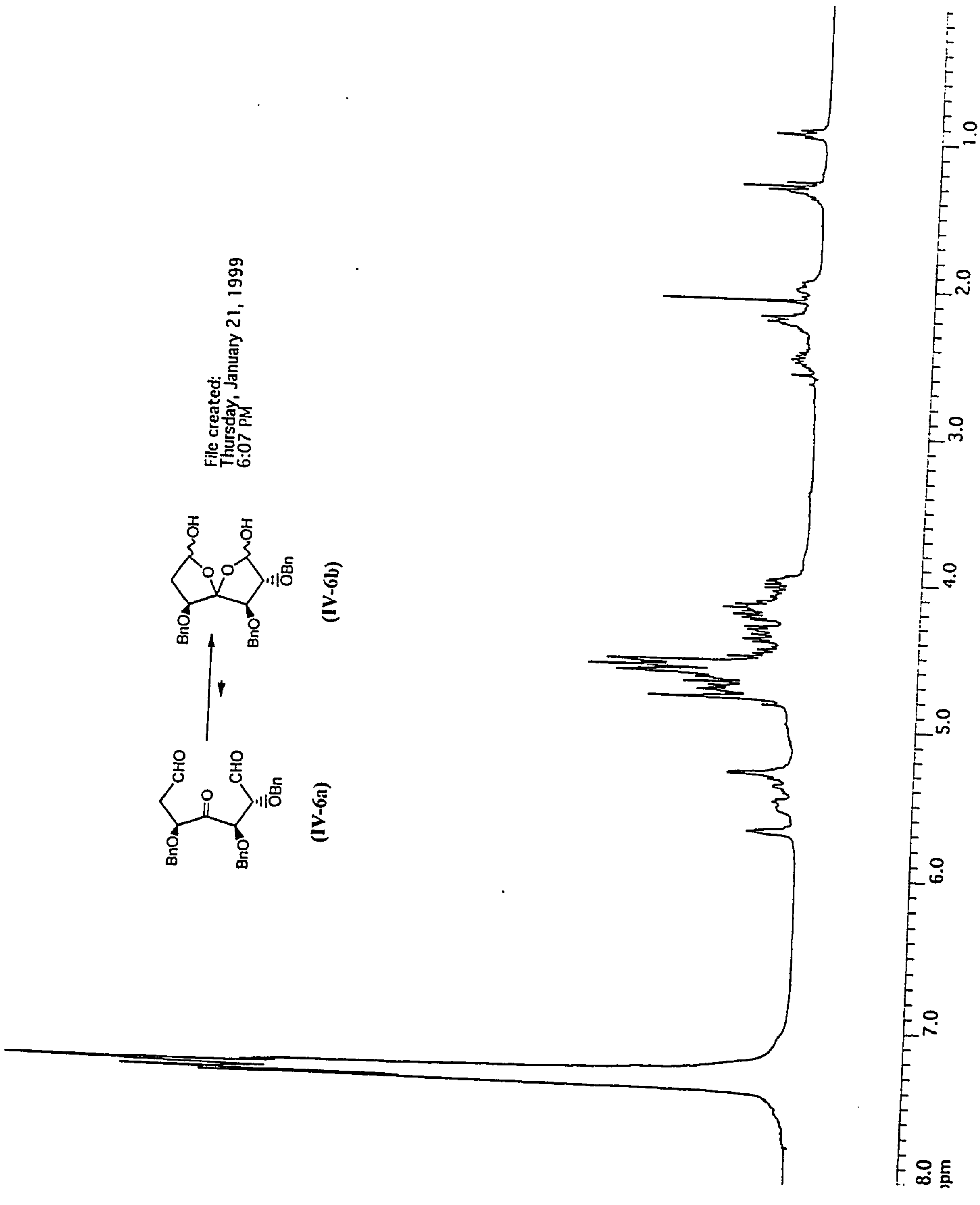
(IV-15)





(IV-15)

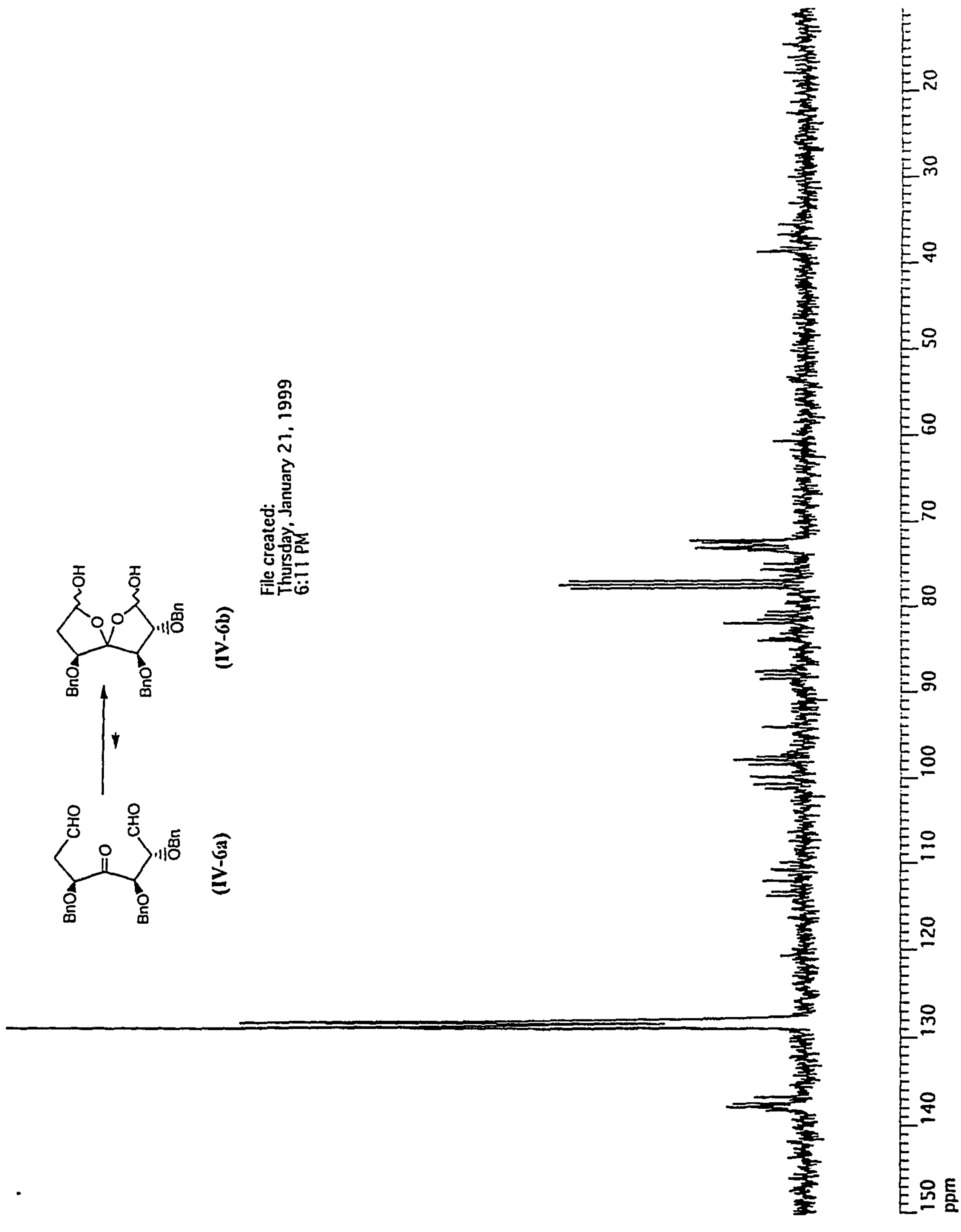




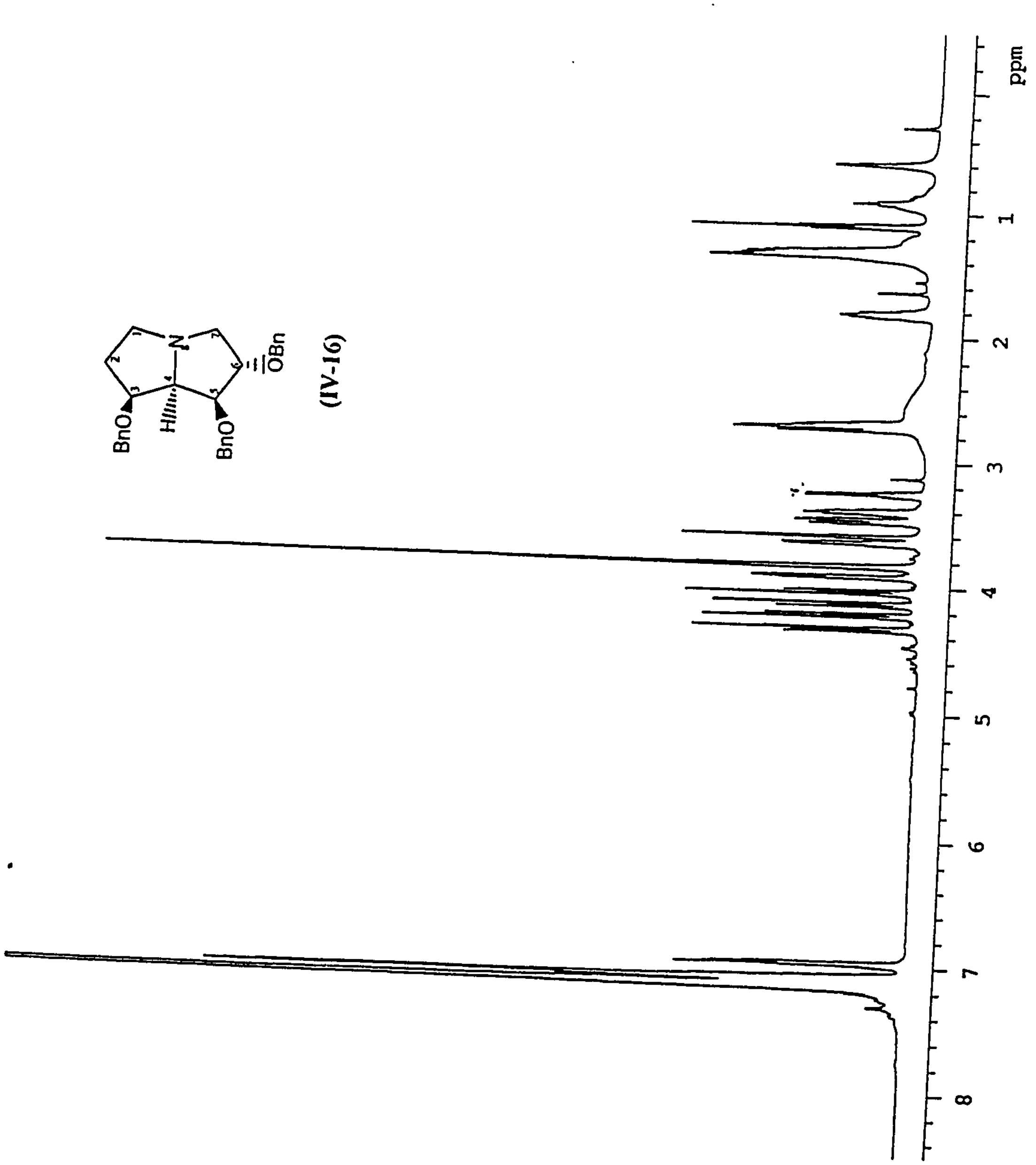
(IV-6a)

(IV-6b)

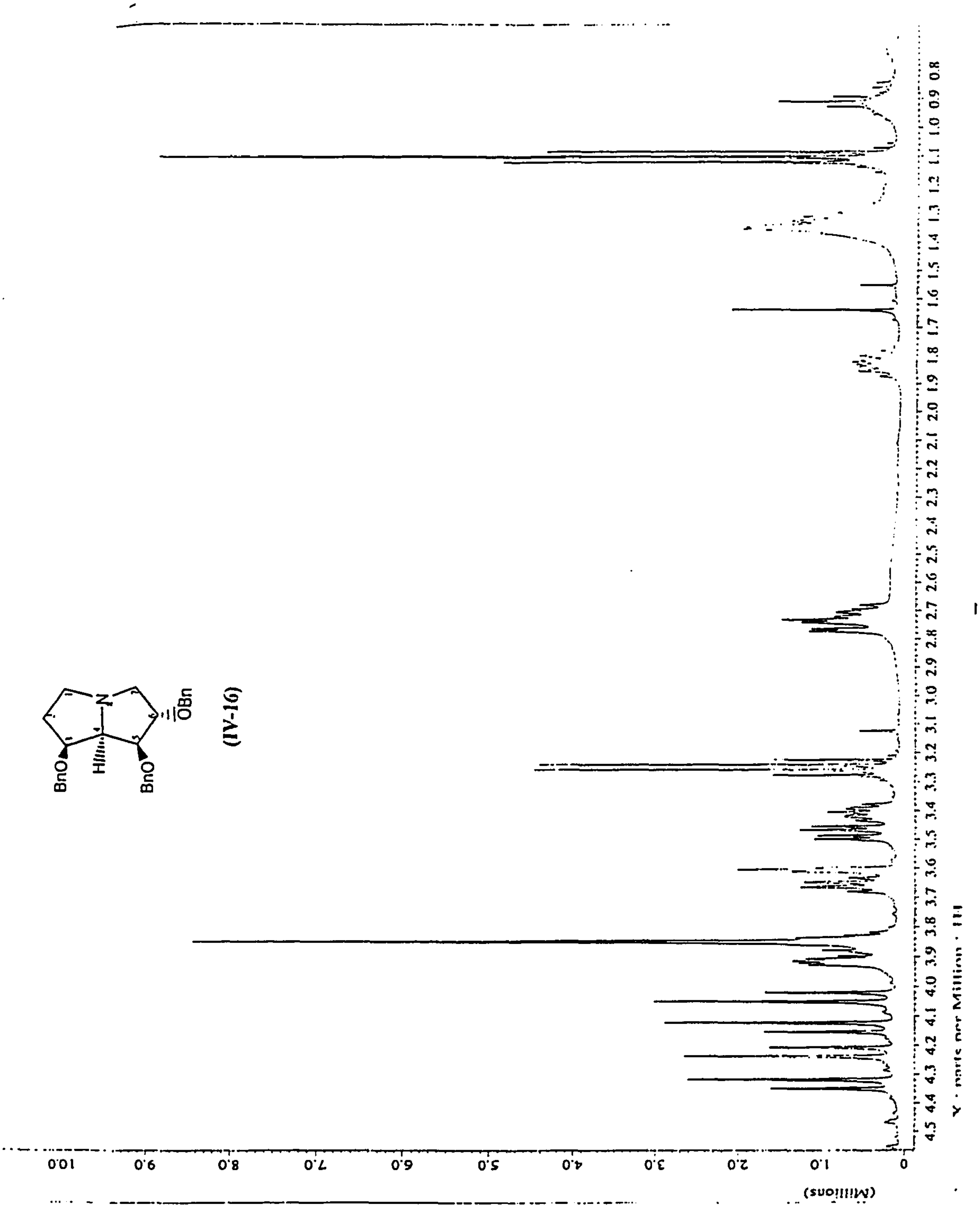
File created:
Thursday, January 21, 1999
6:07 PM



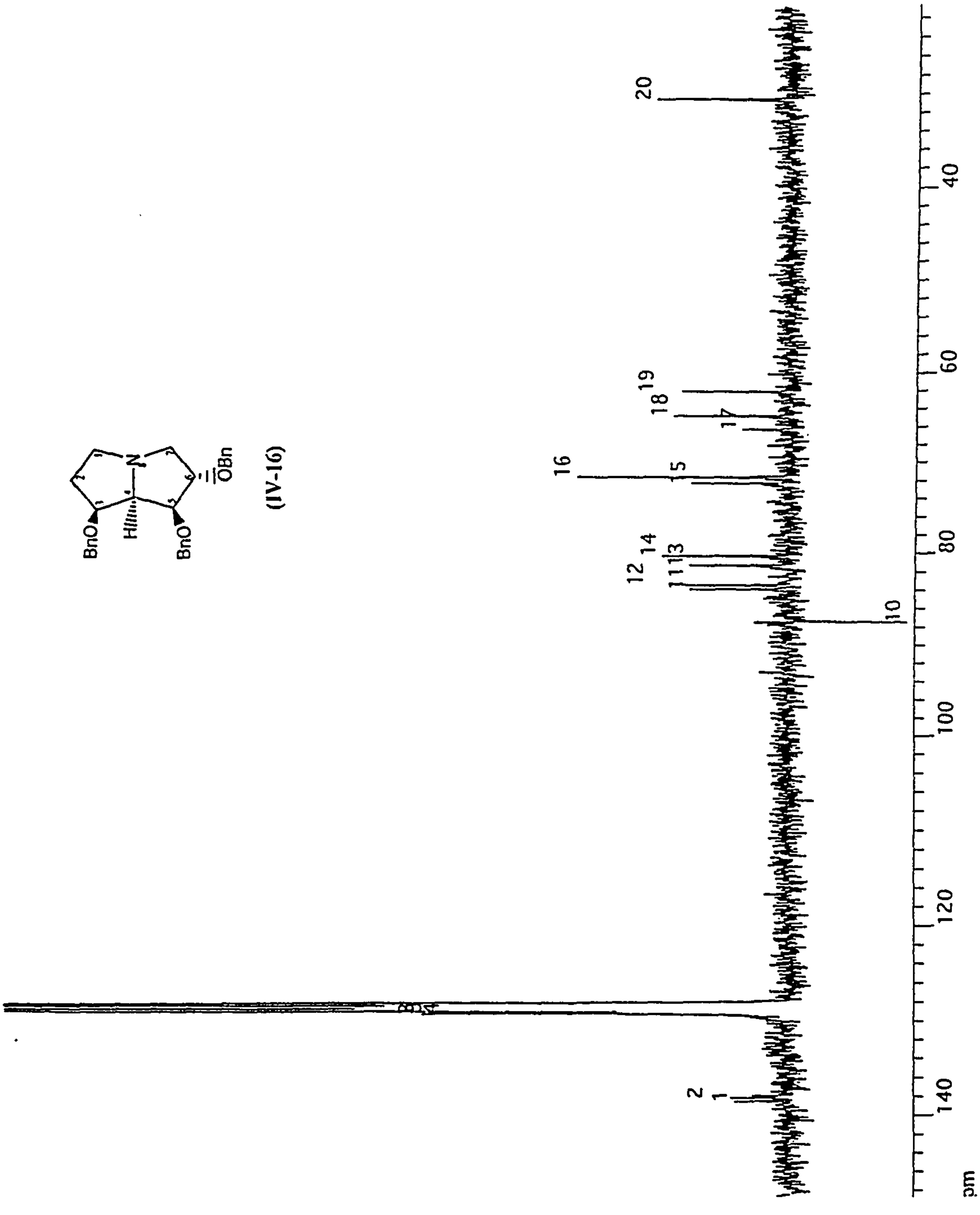
BnO
CHO
O
BnO
CHO
OBn
(IV-6a)
BnO
OH
O
O
BnO
OH
OBn
(IV-6b)
File created:
Thursday, January 21, 1999
6:11 PM
20
30
40
50
60
70
80
90
100
110
120
130
140
150
ppm



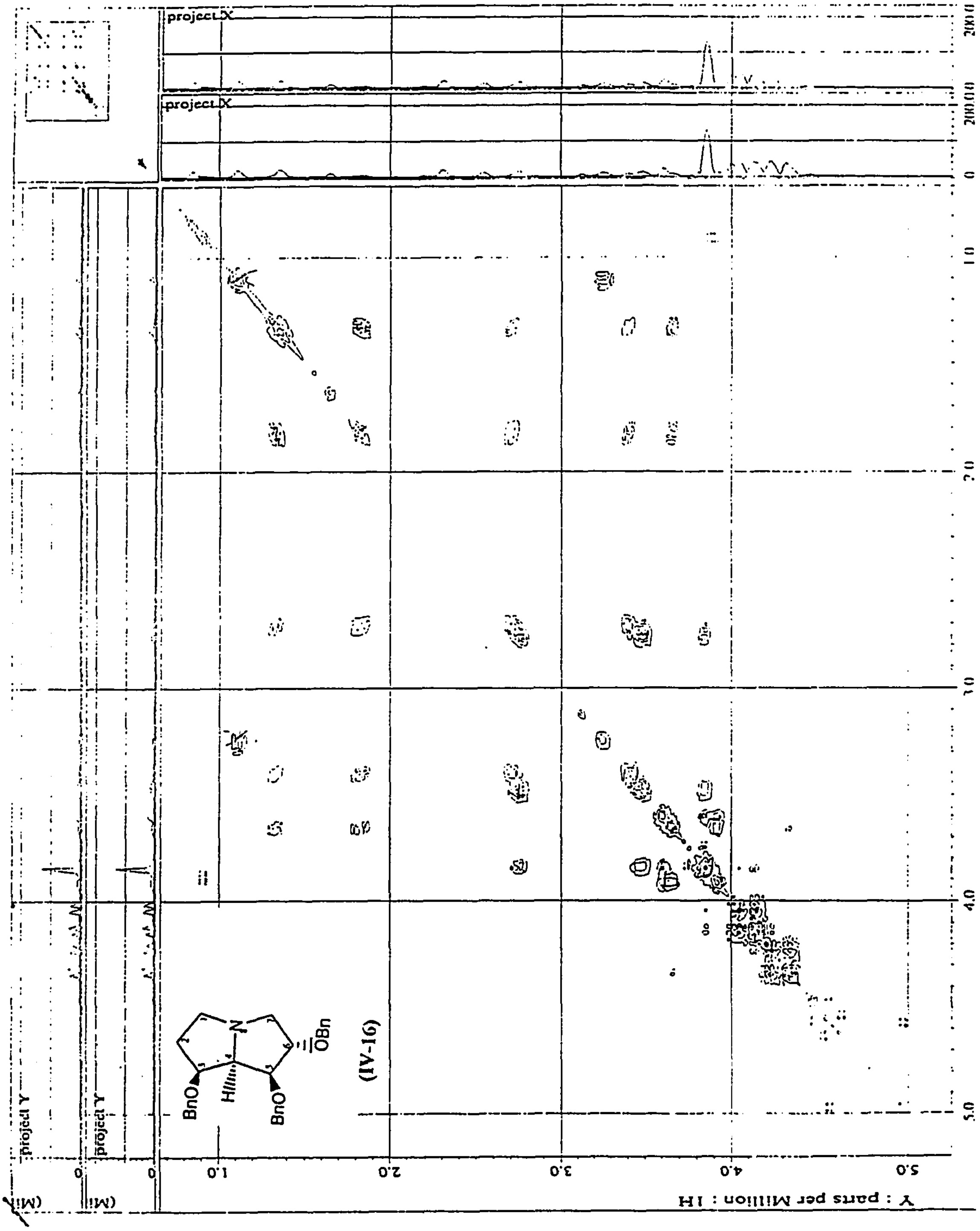
(IV-16)


BnO
H
N
OBn
BnO
X : parts per Million : 1H
4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6 1.5 1.4 1.3 1.2 1.1 1.0 0.9 0.8
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
(Millions)

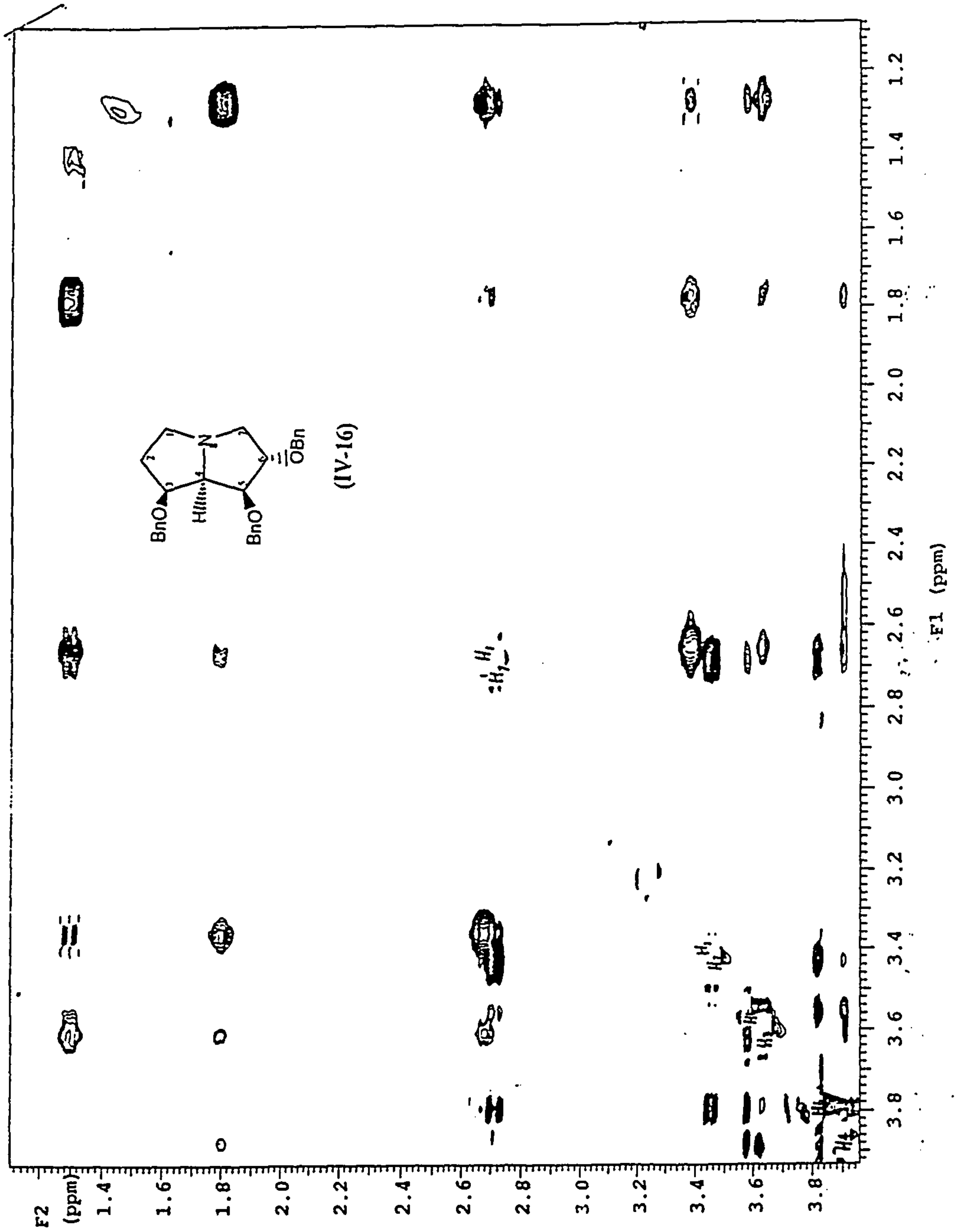
(IV-16)


BnO
H
N
OBn
BnO
20
19
18
17
16
5
14
13
12
11
10
2
1
40
60
80
100
120
140
pm

(IV-16)


projectX
projectX
projectY
projectY
Y : parts per Million : 1H
1.0
2.0
3.0
4.0
5.0
BnO
H
BnO
N
OBn

(IV-16)


BnO
H
BnO
N
OBn
H1
H1
H4
H1
H2
H3
H4
F2 (ppm)
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
F1 (ppm)

(IV-16)

References:

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